IMPROVING TIME TO PATIENT ACCESS TO INNOVATIVE ONCOLOGY THERAPIES IN EUROPE

EVERY DAY COUNTS

VINTURA

JULY 2020

Colophon

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In collaboration with:
ASC Academics
Hague Corporate Affairs

About this report

This report presents the outcomes of the “Time to Patient Access” initiative. The ambition of this initiative is to bring together stakeholders across Europe and to establish a common understanding of causes of delays in patient access to new oncology treatments. It also intends to find the common ground regarding solutions with the potential to reduce time to patient access. The overall aim of the initiative is to make access quicker, for those therapies that are bringing added value to patients and society, without compromising on careful deliberations and evidence-based decision-making.

The project was initiated and financed by the Oncology Platform (EOP) of the European Federation of Pharmaceutical Industries and Associations (EFPIA). The EOP is a collaboration of eighteen companies from the research-based pharmaceutical industry in Europe, launched in 2016, to combine forces and improve cancer patient outcomes in Europe.

The initiative has been carried out with the support of a consortium led by Vintura and comprising ASC Academics and Hague Corporate Affairs. The consortium worked together with two of Europe’s leading experts in health economics and HTAs: Prof. Lieven Annemans (Ghent University) and Prof. Maarten Postma (University of Groningen).

This publication is the result of a multi-stakeholder collaboration gathering views through sounding board meetings and interviews. It does not necessarily reflect the positions of the individual organisations or people involved.

The publication has the explicit endorsement from the following organisations:

Executive summary

Unequal access to innovation in oncology

The unprecedented speed of innovation in oncology provides an important opportunity for further improvement of outcomes for cancer patients. Yet, no value is derived from innovation if patients for whom a new therapy is intended cannot have access to it. In fact, tremendous differences exist in patient access to innovative oncology treatments across European countries. Access to new oncology therapies varies significantly from country to country on three dimensions of access:

- Out of all oncology therapies with a European marketing authorisation, the proportion of therapies that receive **Market Access,** i.e. are reimursed through social health insurance schemes, ranges from as low as 7% to as high as 98%.
- After receipt of a European marketing authorisation, the **time to Market Access** ranges from as low as 86 to almost 1,000 days.
- After twelve months of formal reimbursement, the relative level of **Patient Access*** ranges from as low as 22% to as high as 81%.

These differences undermine the ambition to promote equal access to healthcare and indicate opportunities for improvement.

A multi-stakeholder approach

This report represents the collective thinking of a group of over 30 organisations, covering health technology assessment (HTA) bodies, healthcare professional associations, patient organisations, policy makers, former politicians, payers and pharmaceutical companies concerned about timely and equal access throughout Europe. The aim is to bring stakeholders across Europe together around opportunities to improve time to patient access for innovative, value-adding oncology therapies. It focusses on the dimensions of time to Market Access and Patient Access.

To start, stakeholders aligned on gathering information through:

- Six country case studies to identify delaying factors, solution areas and best practices.
- A benchmark analysis to compare patient access after twelve months of reimbursement in ten European countries.
- A mapping of the differences in evidence requirements in the six case study countries.
- An analysis of the health gains that can be achieved if time to market access was reduced.

The findings were reviewed and discussed over a series of multi-stakeholder sounding board meetings that allowed for combining different perspectives and providing a comprehensive and unbiased overview of challenges and areas in which joint action is needed.

For patients, every day counts

During reimbursement discussions, time to market access can become an abstract objective. Whereas for patients, every day counts. Two case studies on different oncology therapies are presented in the report to show the actual impact of reducing delays in reimbursement decision-making and hence the time it takes for patients to access new therapies. The analysis illustrates the number of patients that could have been treated and the improved quality of life they could have gained if access timelines were shortened. These two case studies serve as a reminder of our common objectives and the urgency of addressing delays where possible.

* Calculated as the cumulative use in the first 12 months after reimbursement, relative to that of the country with the highest use. This was done for thirteen individual oncology therapies, after which the average was used as an indicator (see Section 1.3)

The ten key factors delaying patient access
There are ten factors that cause most delays in patient access to new cancer medications.

These are related to process, reimbursement criteria and health system readiness.

Proces

Process, i.e. how stakeholders organise the series of steps to take

1. **Late start of application and submission.** The national access process may start late compared to the European Union (EU) marketing authorisation, due to country regulations on the start of the process and/or manufacturers submission timelines under the influence of external reference pricing.

2. **Lack of adherence to maximum timelines.** There is not always a clear set of rules around the timelines for decision-making on national pricing and reimbursement, or these rules are not complied with, despite the maximum of 180 days set by the EU Transparency Directive.

3. **Multiple layers of decision-making.** After a national decision or recommendation on reimbursement, subnational decision-makers may make their own decisions on reimbursement or budget allocation, leading to duplication, in-country disparities and delays.

Reimbursement criteria

Reimbursement criteria, i.e. what information stakeholders use to define value

4. **Different evidence requirements across Europe.** The extent to which evidence for the clinical assessment is considered robust or acceptable varies greatly across HTA bodies in Europe, thereby prolonging alignment and/or leading to country-specific data collection.

5. **Lack of clarity of national requirements.** Within countries, requirements for the clinical- and cost-effectiveness assessment are not always consistently applied, which allows for a tailor-made assessment but also leads to unpredictability and prolonged alignment.

6. **Evidence gaps.** Meeting HTA evidence requirements is getting more difficult given the characteristics of today's oncology therapies, leading to evidence gaps, uncertainty about the value of the therapy and prolonged reimbursement discussions.

7. **Misalignment on value and price.** Uncertainty about the value of the therapy leads to misalignment and long negotiations on value and price between national decision-makers and pharmaceutical companies, especially in the absence of mechanisms to deal with uncertainty.

Health system readiness

Health system readiness, i.e. to what extent stakeholders integrate the therapy in clinical practice

8. **Insufficient budget to implement decisions.** There is not always enough budget to implement a positive reimbursement decision, causing implementation to be delayed or resulting in budget depletion at the end of the budgeting period, putting a negative pressure on prescription and use.

9. **Low frequency of clinical guideline updates.** Clinical guidelines do not always include the most recent therapeutic innovations, leading to delays in HTA decision-making and hampering prescription and use due to a lack of clarity on the positioning of the new therapy in the treatment pathway.

10. **Suboptimal healthcare infrastructure.** Suboptimal organisation of healthcare systems in general and oncology care pathways in particular may lead to problems in absorbing and using a new therapy in the most optimal way.

The six priority areas for reducing the time to patient access

To address these factors, multi-disciplinary and concerted actions are needed in six priority areas. All stakeholders are invited to engage in a dialogue and to find novel ways of working together in order to:

PROCESS

1. Align dossier submission timelines

Stakeholders ought to create a joint understanding of the pros and cons of external reference pricing and explore alternatives. Furthermore, pharmaceutical companies should build HTA capabilities to prevent these from becoming the key bottleneck in aligning dossier submission timelines across countries in Europe.

2. Shorten reimbursement timelines

Optimal alignment between parties prior to European marketing authorisation, allowing for dossier submission and assessment as soon as possible after marketing authorisation, taking steps in parallel rather than sequential, and keeping the layers of decision-making to a minimum can reduce time to patient access in countries. Involving patients and making timelines transparent helps in maintaining a sense of urgency at every step of the process.

REIMBURSEMENT CRITERIA

3. Align evidence requirements

Much like the European Medicines Agency (EMA) has improved the efficiency for granting market authorisations, European HTA alignment on clinical assessment (after which appraisal takes place at national level) would improve the timelines to patient access. In addition, European cooperation and alignment would reduce duplication of efforts and allow for more efficient use of scarce human and financial resources.

4. Be adaptive to rapidly evolving innovation

Reimbursement criteria need to be clear to allow for predictability, while at the same they should be flexible to enable applicability to a variety of therapies and cases. Furthermore, a comprehensive system of horizon scanning, early collaboration, managed access schemes, and real-world data generation should be in place to proactively manage today's challenges and avoid delays, e.g. using novel pricing and payment models.

HEALTH SYSTEM READINESS

5. Improve healthcare infrastructures

Pricing and reimbursement decisions should lead to an update of the guidelines and budget provisions. Furthermore, to improve screening and diagnosis, clear roles and responsibilities need to be assigned. When it comes to treatment, centres of excellence for (rare) cancers should be accessible to all patients, e.g. with the use of e-health solutions.

6. Strengthen collaboration between all stakeholders

As important as it is obvious: stakeholders must collaborate. In each of these priority areas, a concerted effort is needed, as none of today's challenges can be addressed by a single stakeholder. Current early dialogues and scientific advice should evolve into early collaboration to enable a joint quest for solutions to potential access challenges. In addition, controversial topics that further constrain stakeholder relations need to be addressed proactively.

A call for further dialogue and joint problem-solving

This report provides a high-level overview in this complex domain. It is a starting point. It is a call for further dialogue, analysis and joint problem-solving by all relevant stakeholders in order to further explore the six priority areas. To reduce the immense inequalities in patient access between European countries we need to find a common understanding and a common perspective. This is needed because all stakeholders are part of the current system in which we operate and none of the stakeholders involved can solve today's challenges single-handedly. We need a collaborative approach now. For patients, every day counts.

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1. Introduction

1.1 The high speed of innovation in oncology

We live in times when speed of innovation for cancer patients is unprecedented. This is shown by an increasing number of European marketing authorization in oncology and the fact that nearly 40% of drugs in development* are oncology therapies (Hofmarcher, et al., 2019) (Albrecht, B; Andersen, S; Chauhan, K; Graybosch, D, 2018).

The new wave of scientific innovation is generating an unprecedented level of choice and promise in cancer treatments. Increasingly, therapy selection in oncology is tailored to the individual patient and disease characteristics, to improve the likelihood of patients responding to treatment. The body's own immune system can be activated to attack the tumor. And gene and cell-based therapies provide a potential cure.

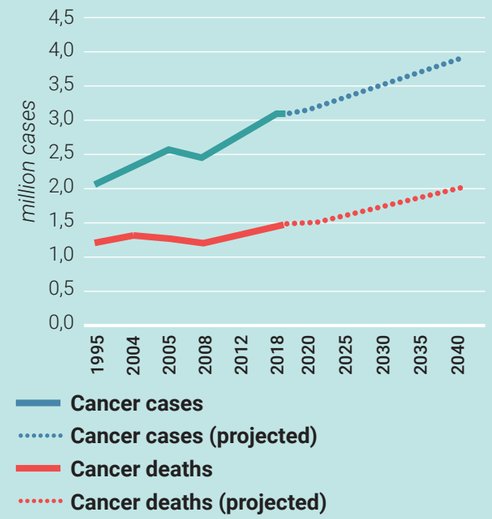
These pharmaceutical innovations contribute to significant advances in cancer outcomes, together with advances in e.g. effective prevention, screening programmes, radiotherapy and surgical care.

Today, the number of lung cancer patients that is alive one year after diagnosis is more than ten times higher than in 1995, when only five out of 100 lung cancer patients were alive after one year (Schiller, 2018). This is just one example of how cancer survival rates have increased dramatically over the past 35 years (Cancer Research UK). As a result, the number of cancer deaths in Europe shows slower growth than the number of cancer diagnoses (Hofmarcher, et al., 2019). This is illustrated in Figure 1.

Fig. 1

Number of cancer deaths in Europe is increasing

Although at a slower pace than the number of cancer diagnoses



Source: Hofmarcher, et al., 2019

* Defined as Phase I – III clinical trials.

Nevertheless, cancer incidence is growing. The number of people diagnosed with cancer across Europe has risen by approximately 50% over the past two decades. Today, cancer is responsible for one in every four deaths in Europe, making it the second leading cause of death and disability after cardiovascular disease. The impact on individual patients, their families and society is tremendous (Hofmarcher, et al., 2019).

Still, improvements in services and treatments are leading to better outcomes. In lung cancer, for example, 13,296 more patients were alive for at least five years following a diagnosis in 2014, compared to those diagnosed in 2004 (Hofmarcher, et al., 2019). However, more efforts are needed to ensure every patient has access to the latest standard of care and treatment no matter in which European country they reside.

1.2 Three milestones in bringing innovative therapies to patients

Innovation has no value if patients for whom new therapies are intended cannot have access to them. Once a new treatment has gone through a process of ten years of research and development on average, three further milestones have to be reached before patients have access to it (see Figure 2):

1. European **Marketing Authorization** needs to be granted, confirming the quality, the safety and the efficacy of the therapy.
2. Authorities within countries have to decide on **Market Access** meaning reimbursement of the therapy under an insurance or reimbursement scheme, in order to make the intervention financially accessible to all patients*.
3. Once reimbursed, **Patient Access** must be achieved, meaning that the patients they are intended for use the innovations after prescription by a specialist, in accordance with their marketing authorization, reimbursement guidelines and the latest scientific insights.

1.3 European inequalities in reimbursement and use of innovations in oncology

Following advice from the European Medicines Agency (EMA), the European Commission (EC) grants a centralized marketing authorization covering all European Union (EU) Member States. This takes away the need for pharmaceutical companies to seek marketing authorization for new therapies from each Member State separately.

By contrast, reimbursement decisions are organized by national and sometimes even sub-national (regional) authorities. These authorities use different processes and requirements, leading to different decisions and considerable inequalities in patient access throughout Europe. These inequalities can be found in all three dimensions of patient access:

- **Market Access**, which refers to the proportion of oncology therapies with a European marketing authorization that subsequently receive a positive reimbursement decision. This rate ranges from as low as 7% in Latvia to as high as 98% in Germany (IQVIA, 2020).
- Time to **Market Access**, which refers to the number of days between a European marketing authorisation and a formal positive reimbursement decision (this excludes early access schemes during which certain patients may receive reimbursement before the formal HTA process is finalized). The difference between the country where patients gain access reimbursement first (Denmark, 86 days on average) and the country where patients gain access reimbursement last (Latvia, 981 days on average) is close to 2.5 years. This means that patients in Latvia had to wait 2.5 years before being able to receive treatments that benefited the lives of patients in Denmark within less than three months following marketing authorization (IQVIA, 2020).
- Relatively unexplored is the domain of Patient Access. Having reimbursement in place does not necessarily mean that the medicine is prescribed, i.e. that patients are actually treated with the new therapy. There are remarkable differences between countries in the actual use of new oncology therapies in clinical practice, once

* For the purpose of this report, reimbursement refers to a formal reimbursement decision, thereby excluding early access schemes as these schemes often provide reimbursement on a restricted or case-by-case basis without completion of the formal HTA procedure.

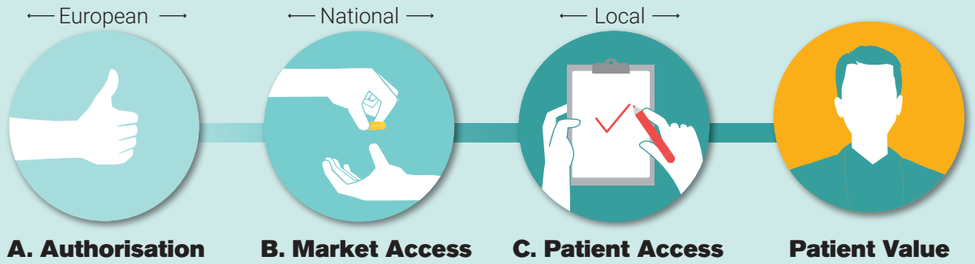
Fig. 2

After ten years of research and development:

Three milestones must be reached to bring innovative therapies to patients

Patient acces milestones

Milestones A, B & C:



A European marketing authorization is granted when the European Medicine Agency (EMA) positively evaluated:

- ✓ **Quality:** Is the quality of the manufacturing process up to standards?
- ✓ **Safety:** Is the therapy safe?
- ✓ **Clinical efficacy:** Is the therapy effective?

This supra-national authorization takes away the requirement to seek marketing authorization for new medicines from each Member State separately.

Authorities within countries need to make transparent and evidence based decisions on reimbursement of oncology therapies, as these are public healthcare expenditures. To inform reimbursement decisions for innovative oncology therapies, typical questions that need to be answered by national HTA bodies are:

- ✓ **Medical need**: Does this therapy address a health need?
- ✓ **Relative clinical effectiveness:** Is it more effective than current therapies?
- ✓ **Cost effectiveness:** Is the price a good reflection of the added value?
- ✓ **Budget impact:** Can we afford the overall costs of this therapy?

This is done separately by each country. How countries make these decisions varies, leading to significant disparities in patient access throughout Europe.

Once reimbursed, innovations must be prescribed to the patients they are intended for, who must use them well. This requires:

- ✓ **Administration:** Finalization of administrative procedures and allocation of budget
- ✓ **Integration:** Adequate health system infrastructure and oncology care pathways
- ✓ **Prescription:** Prescriber awareness
- ✓ **Use:** Patient access to the right expertise (geographical, financial, awareness)

Source: Efpia 2020

reimbursement is in place. After twelve months of formal reimbursement, the relative cumulative use* ranges from as low as 22% in the Netherlands to as high as 81% in France. A description of the methodology used to quantify country differences in this dimension of patient access is provided in Box 1.

This report focuses on:

- **Time to Market Access,** i.e. delays in reimbursement, and
- **Patient Access,** i.e. actual prescription, and use.

Figure 3 highlights the three access challenges that patients in European countries are facing in these two dimensions. It shows that none of the countries included in this analysis has optimal access in terms of both time to Market Access and Patient Access.

A country that comes very close to this optimal situation is Germany. German patients are guaranteed immediate reimbursement after a therapy receives a European marketing authorization, while the decision-making about permanent reimbursement starts in parallel**. This explains why Germany is among the countries with the shortest time to Market Access in Europe. However, the number of patients that have access to the therapy after 12 months is relatively low. The fact that a therapy is very new when it becomes available in Germany, may explain why it takes longer before it is actually prescribed to patients: the body of evidence (scientific publications, clinical guidelines) is still developing and both prescribers and patients need to become familiar with the new therapy. Furthermore, physicians may be reluctant to prescribe the new therapy, until it has gone through the formal HTA process. Another explanation may be the high proportion of oncology therapies with a European marketing authorization that receives a positive reimbursement decision in Germany (98%). This may imply that the number of alternative therapies in Germany is higher than in other countries, leading to a lower clinical use per individual therapy.

The Netherlands is an example of a country with the first access challenge: a relatively short delay but low patient access. On average, innovative oncology therapies in the Netherlands are reimbursed 234 days after European marketing authorization. However, in the 12 months following this decision, and compared to the country with the highest patient access, only 20% of the patients receives the therapy (compared to the number of patients that received the therapy in the country with the highest real-world access). This may be explained by the fact that after the national reimbursement decision, contracts need to be negotiated with individual hospitals (operating in a context of budget constraints) before the therapy can be prescribed. Another explanation could be the fact that it takes a long time for new therapies to be included in clinical guidelines.

Poland is an example of a country with the second access challenge: long delays and low patient access. In Poland, it takes on average 891 days before an innovative oncology therapy is reimbursed. And in the first 12 months after reimbursement, only 24% of the patients have access to the therapy. This may be explained by the fact that requests for reimbursement are submitted later in Poland, that the decision-making process is long, and/or that positive reimbursement decisions are made for a subgroup of the overall patient population for which a European marketing authorization was granted (which may be driven by budget impact considerations in a context of a relatively low GDP).

An example of a country with the third access challenge is France. In France, on average 80% of patients have access to an innovative therapy after the first 12 months of formal reimbursement. Yet it takes a long time before this formal reimbursement is in place: 579 days on average. Both characteristics may be explained by the French 'Temporary Authorization for Use' program (ATU). This early access program does not equal formal reimbursement, as it is not preceded by a formal HTA process and is not available for all therapies or patients*. Nonetheless, it allows (some) patients to have access prior to formal reimbursement. Once this formal reimbursement is in place, patients and prescribers are more likely to be already familiar with a therapy, because they gained experience with the therapy through the ATU. This may explain the high level of patient access in the first 12 months after formal reimbursement.

The four examples provide an overview of the different access challenges that European countries are facing. A few potential factors causing delays in time to patient access are provided, but more research is needed to assess the specific factors at play in a specific country.

The present report can help in this endeavor. It provides an overview of the 10 key factors delaying time to patient access across European countries. It also provides six solution areas for eliminating these delays. It can be used by stakeholders to make a detailed assessment of the factors at play in their country and the relevant solutions to deploy: an endeavor that requires an effort from all stakeholders in the healthcare system.

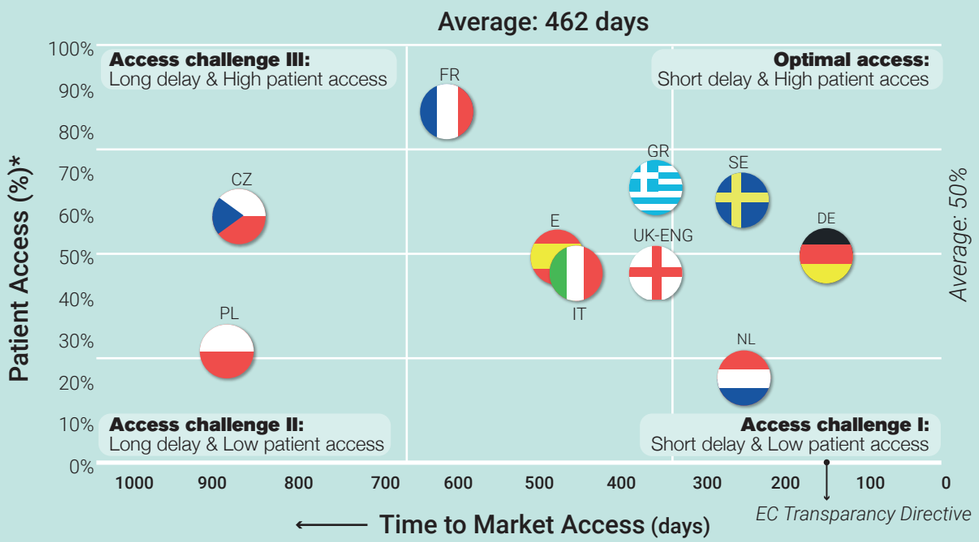
* Calculated as the cumulative use in the first 12 months after reimbursement, relative to that of the country with the highest use. This was done for thirteen individual oncology therapies, after which the average was used as an indicator.

** Within six months, a health technology assessment is conducted, after which the actual reimbursement price is negotiated. This price replaces the initial price (list prices set by pharmaceutical companies) one year after launch.

* In fact, this early and temporary access mechanism may sometimes even delay a formal reimbursement decision (Degrassat-Théas, Paubel, Parent de Curzon, Le Pen, & Sinègre, 2013)

Fig. 3

Within Europe, huge inequalities exist in time to Market Access and Patient Access to new oncology therapies



* Cumulative use after 12 months of reimbursement, relative to the country with the highest cumulative use

Sources QVIA, 2020 and Ventura, 2020 (see Box 1)

Box 1

The Patient Access Indicator

Whilst we know the rate of Market Access and time to Market Access for innovative oncology therapies quite well based on the annual EFPIA W.A.I.T. Indicator Study (IQVIA, 2020), no analysis was available of European differences in actual use after reimbursement (Patient Access). To address this information gap, a European benchmark analysis was made to compare post-reimbursement use between countries, for a set of innovative oncology therapies.

For this benchmark, 'use' was measured by analysing volume sold per month (or patients treated per month, based on volume sold), per capita, using routinely collected business information from pharmaceutical companies and data providers. 'Post-reimbursement' was defined as the phase that starts when the first patient is treated under a formal reimbursement scheme. Therefore, early access schemes are excluded, as these schemes often reimburse on a case-by-case or restricted basis without completion of the formal HTA process.

Ten countries were included: Czech Republic, England, France, Germany, Greece, Italy, Netherlands, Poland, Spain and Sweden. The thirteen oncology therapies included cover Leukaemia (n=4), Breast cancer (n=3), Lung cancer (n=3), Bladder cancer (n=1), Multiple myeloma (n=1), Melanoma (n=1), Non-melanoma skin cancer (n=1) and Ovarian cancer (n=1): alectinib, atezolizumab, cobimetinib, daratumumab, ibrutinib, midostaurin, olaparib, osimertinib, pertuzumab, trastuzumab-emtansine, venetoclax, and vismodegib. Annex B provides a detailed description of how countries and therapies were selected.

Furthermore, the country figures were standardized to correct for epidemiological differences. However, this correction is not included in the findings presented, because the reliable and comprehensive epidemiological data from the IARC Global Cancer Observatory are available at the level of the main cancer types. Using this data would not provide an accurate correction for epidemiological differences between countries, given the specific indications of the therapies in scope of this analysis.

Subsequently, per therapy, the cumulative use at twelve months post-reimbursement was expressed as a relative use, compared to the country with the highest use of that therapy. And finally, per country, the average relative use across all therapies was calculated to arrive at one single indicator of post-reimbursement use compared to other countries. This information was combined with the latest information on delays in reimbursement (IQVIA, 2020; see Figure 3).

Two important aspects should be considered when interpreting the findings of the analysis. First, **the benchmark illustrates differences rather than best practices.** High clinical use for a specific therapy does not equal optimal access. High clinical use can also be a symptom of a suboptimal access situation, e.g. when a more advanced treatment option such as stem cell transplantation (in the case of haematology) is not available or accessible. Countries with the highest clinical use per therapy were set as the benchmark country (100%) to enable comparison, not to set a standard or best practice. However, since the benchmark covers multiple therapies in multiple indications, it provides a good indication of health system factors posing a barrier to patient access.

Second, the outcomes serve as the start of further research and discussions on European inequalities regarding post-reimbursement clinical use. They give a quantitative overview of the differences, without explaining the reasons behind these variances.

A detailed description of the methodology can be found in Annex B.

1.4 A multi-stakeholder perspective on challenges and solutions: the methodology

In order to connect all relevant stakeholders, this report combines the different perspectives and provides a comprehensive and unbiased overview of challenges and areas in which joint action is needed. It is the result of a collaborative approach by health technology assessment (HTA) bodies, healthcare professional associations, patient organizations, policy makers, former politicians, payers and pharmaceutical companies. Different methodologies and sources of information were used to develop and validate the content of this report.

Country case studies on delaying factors and solutions

Little is known about the reasons behind variances and delays in time to patient access. Therefore, case studies were conducted in six European countries which together represent the diverse access contexts in Europe. Together, the group of six countries should represent the diverse access contexts in Europe and a set of selection criteria was defined to guide the country selection. Countries selected were England, Italy, the Netherlands, Poland, Portugal and Sweden. Document reviews and interviews with regulators, payers, former politicians, HTA bodies, healthcare professional associations, patient organizations, industry organizations and experts allowed for an in-depth understanding of delaying factors, best practices and potential solution areas in these countries. Content analysis of the country findings allowed for identification of a first set of delaying factors and solution areas, potentially applicable to a broader European context. Details about the methodology and summaries of the six country profiles can be found in Annex A.

Patient Access Indicator

An analysis of patient access was undertaken to identify European differences in the use of new oncology therapies twelve months after reimbursement. Outcomes are presented in Chapter 1, section 1.3 (Figure 3). The methodology is described in detail in Annex B.

Mapping of European differences in evidence requirements

One cause for delays in patient access is the differences in evidence requirements across Europe. A comparative analysis of evidence requirements was performed for EMA and HTA bodies in the six case study countries. A detailed account of the differences and the level of alignment and predictability across agencies is provided in sections 4.4 and 4.5 (Figures 9 and 10). The methodology is described in detail in Annex C.

Impact analysis of improved time to market access

To make the potential impact of reducing delays in reimbursement decision-making and hence the time it takes for patients to access new therapies more tangible, an impact analysis was performed. The findings are presented in sections 3.1 and 3.2. They serve as a reminder of our common objective and the urgency of addressing delays where we can. The methodology is described in detail in Annex D.

Multi-stakeholder Sounding Board

A European multi-stakeholder sounding board was established to discuss and validate the project set-up and findings, and to place the information generated from case study countries into the larger perspective of all European Member States. In addition, the sounding board allowed for capturing different perspectives to ensure balanced outcomes. Over the course of the initiative, over 25 organizations operating at the European and/or national level participated in one or more sounding board meetings. An overview of all stakeholders that contributed to the initiative, e.g. through participation in interviews or one or more sounding board meetings, can be found in the list of Contributors at the end of this report.

2. The diversity of European access systems

CONTRARY to the unified marketing authorization process for EU Member States, reimbursement decisions are made by authorized bodies within the Member States. This is because medical need, effectiveness compared to the current standard of care, cost-effectiveness and budget impact are often influenced by local characteristics and are in the remit of each Member State.

The national settings in which these reimbursement decisions are made vary, in terms of economic context, levels of decision-making involved and main criteria for reimbursement.

2.1 Economic context

The latest data from the Organization for Economic Cooperation and Development (OECD) from 2017 clearly shows the European differences in economic context:

- Absolute healthcare spending ranges from EUR 5,300 per capita in Germany to EUR 1,300 per inhabitant in Romania.
- Relative healthcare spending as a % of overall GDP, is more than 2 times higher in France (11.3%) than in Romania (5.2%).
- Absolute pharmaceutical spending ranges from EUR 286 per inhabitant in Denmark to EUR 740 per inhabitant in Germany.
- Relative pharmaceutical expenditures as a % of overall GDP, is 3.5 to over 5 times higher in Greece or Bulgaria (2.2% and 3.3% respectively) compared to Luxembourg (0.62%)*.

* In these figures (OECD, 2020), based on 2017 data, healthcare spending includes government spending, compulsory and voluntary insurance schemes. Out-of-pocket payments are excluded. Pharmaceutical spending covers prescription medicines and over-the-counter products. Pharmaceuticals consumed in intramural settings are excluded.

2.2 Levels of decision-making involved

The Treaty of the Functioning of the EU leaves the budget and the management of the health system in the remit of Member States (Art. 168), in contrast to other areas of policy such as the internal market. Therefore, the way in which Member States organize and finance their health systems differs considerably. Consequently, European countries have different ways of organizing their reimbursement decision-making. As shown in Figure 4, some countries such as Iceland and Croatia organize price negotiations, assessment, appraisal and budget allocation on a national level. Other countries organize these decisions partly at a national level and partly at a regional level. In most European countries price negotiations, assessment and appraisal take place on a national level but budgets are allocated by healthcare insurers (a single payer institution or different health insurers) or on a hospital level. (WHO, 2018).

2.3 Reimbursement criteria applied

Although HTA bodies generally ask similar questions to inform reimbursement decisions, the specific assessment criteria differ, as does

Fig. 4

The context in which patients acces takes place differs significantly between European countries: levels of decision-making involved for in-patient therapies

Decision-making level for in-patient therapies	National	National & Regional	Regional & National	National & HCI/ Hospital	HCI/ Hospitals & National
Pricing	National	National	National	National	National
Assessment and appraisal	National	National	Regional	National	Insurer
Budget allocation	National	Regional	Regional	Insurer/ Hospital	Insurer/ Hospital
Countries	IS, HR, LV, MT, UK	IT, NO, ES	AT, DK, FI, SE	BE, BG, CZ, DE, GR, HU, IE, LT, PL, PT, RO, CH	EE, FR, LU, NL, SK, SI

*Sources WHO, 2018, OECD/ European Observatory on Health Systems and Policies, 2017, Huic, 2016**

* In Cyprus (CY), pricing negotiations, assessment and appraisal are done at the national level. The level responsible for budget allocation is unknown.

their relative weight in the final appraisal and decision-making. Figure 5 below illustrates the dissimilarities in main reimbursement criteria for European countries. It provides more detail for the six case study countries that focus on different elements such as clinical effectiveness (e.g. Portugal and Italy), cost effectiveness (e.g. England and Sweden), both (e.g. the Netherlands), or clinical effectiveness, cost-effectiveness and budget impact (e.g. Poland).

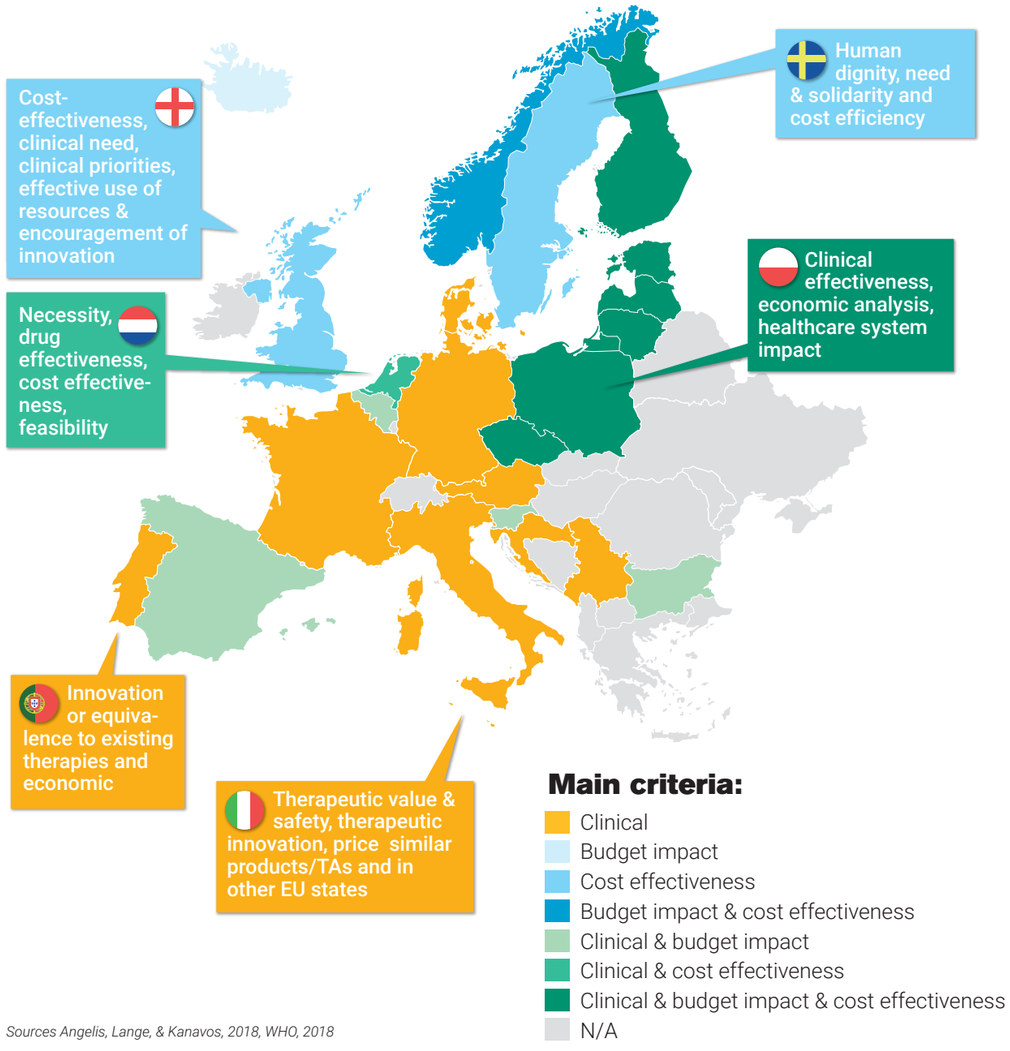
2.4 The five phases of access pathways in European countries

Despite different contexts, European countries generally follow an access pathway comprised of five phases. For governments and payers, these phases form the basis to make evidence-based decisions on public healthcare expenditures.

Fig. 5

Main reimbursement criteria

The context in which reimbursement decisions are made differs significantly between European countries: main reimbursement criteria applied



Sources Angelis, Lange, & Kanavos, 2018, WHO, 2018

1. **Preparation**: Early in the clinical development phase (prior to Phase 3), the early dialogue is an opportunity for pharmaceutical companies to discuss and receive early advice on the development plan. Furthermore, national HTA bodies and payers can apply horizon scanning to identify therapies in the clinical development phase in order to appropriately plan for the potential future assessment, budget implications and use of the therapy.

2. **Application & submission**: An application from the pharmaceutical company and direction from the HTA body on the reimbursement route to follow kick off the national reimbursement process. The HTA dossier is submitted, in line with the country-specific procedures and requirements. Companies can also decide to submit (a part of) their dossier through EUnetHTA, a European collaboration on joint clinical assessments.

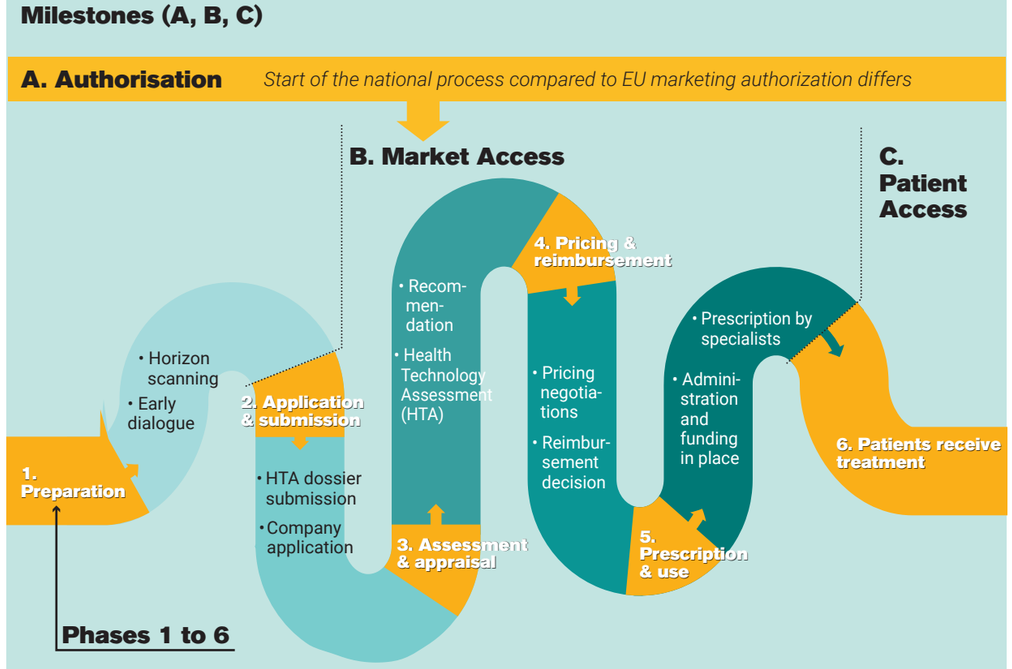
3. **Assessment & appraisal**: Often one committee within an HTA agency is responsible for critically reviewing evidence submissions or synthesizing evidence. Subsequently, another committee considers the wider context and provides advice or a recommendation. Likewise, in the case of EUnetHTA assessments, EUnetHTA synthesizes the evidence on clinical effectiveness, but refrains from conclusions or recommendations as this is done at the national level.

4. **Pricing & reimbursement**: Based on the findings and the recommendation, price

Fig. 6

Despite different contexts, in general European countries follow an access pathway comprising

Five phases to make evidence-based decisions on public healthcare expenditures



negotiations with the pharmaceutical company will start. The pricing negotiations take place with different parties, depending on each country. This could for example be with the government, an organization representing all insurers, or an appointed agency established solely for pricing negotiations.

5. **Prescription & use**: Once the decision on reimbursement has been made, additional steps are often required to implement the decision. These steps take various forms in countries from an official decree, signature, publication, or addition to reimbursement lists, to regional or hospital agreements to procure the drug. In theory, after completion of this process, eligible patients should finally have access to the newly approved medication. This reimbursed access can only materialize when the health system infrastructure and oncology care pathways are adequate, when oncologists have the latest knowledge and expertise, and patients are able to access this expertise.

Phase one can be used to reduce the time needed for phases two to five. Any form of delay in the first four phases therefore ultimately results in a delay in reimbursement. In the last phase of prescription and use, delays or barriers hamper effective access and clinical use (see Figure 6).

3. For patients, every day counts

DURING reimbursement discussions, time to patient access can become an abstract objective. Whereas for patients, every day counts. To make more tangible the potential impact of reducing delays in reimbursement decision-making and hence the time it takes for patients to access new therapies, an impact analysis was carried out to answer the question: what could be gained by ensuring earlier Market Access? The methodology of this analysis is introduced in Box 2.

The findings show the immense gains from improving time to market access and serve as a reminder of our common objective and the urgency of addressing delays where we can.

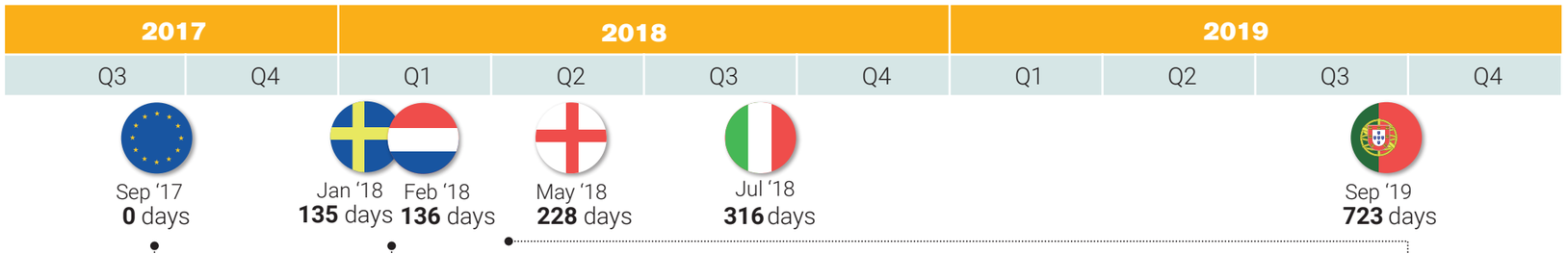
3.1 The case of midostaurin in acute myeloid leukemia

*Impact of earlier time to reimbursement for patients with a rare disease - the case of midostaurin in acute myeloid leukemia**

Midostaurin

Acute myeloid leukaemia (AML): rapid growth of abnormal blood cells that build up in the bone marrow and blood and interfere with normal blood cells. As an acute leukaemia, AML progresses rapidly and is typically fatal within weeks or months if left untreated. Around 80% of patients diagnosed with AML pass away within five tears.

Market Access: dates at which the therapy was reimbursed under a formal reimbursement scheme



What if (scenarios) :

Gains versus standard-of-care:		'Ambitious' scenario A				'Best practice' scenario B				'Basic' scenario C			
Country →		## days between EC authorization and patient access:				Directly after EC authorization: **0**				As fast as the fastest country: **135**				Cf. EC Transparency Directive: **180**			
		SE	**NL**	**UK-ENG**	**IT**	**SE**	**NL**	**UK-ENG**	**IT**	**SE**	**NL**	**UK-ENG**	**IT**
	## additional patients treated →	71	34	1,423	161	n/a	0	580	92	n/a	n/a	300	69
OS	## added months of life →	3,466	1,692	69,867	7,895	n/a	0	28,498	4,522	n/a	n/a	14,709	3,398
EFS	## added months of life without AML getting worse →	367	159	7,399	740	n/a	0	3,018	424	n/a	n/a	1,558	318

* Midostaurin for AML is not reimbursed in Poland. In Portugal it was only reimbursed as of September 2019, resulting in too little uptake information for inclusion in the analysis.

★★★★★

In a highly ambitious scenario,
if midostaurin had been reimbursed in Sweden, the Netherlands, England and Italy directly after EC marketing approval:

1,689 more patients with AML could have been treated.

They could have lived altogether an additional **82,920 months.**

This would have corresponded to **8,665 months** without the disease getting worse.

★★★★☆

In the 'best practice' scenario,
if midostaurin had been reimbursed in the Netherlands, England and Italy after 135 days, like in Sweden:

673 more patients with AML could have been treated.

They could have lived altogether an additional **33,033 months.**

This would have corresponded to **3,433 months** without the disease getting worse.

★★★☆☆

In the 'basic scenario',
if midostaurin had been reimbursed in England and Italy as fast as agreed in the EC Transparency Directive (a condition fulfilled by the Netherlands and Sweden):

369 more patients with AML could have been treated.

They could have lived altogether an additional **18,107 months.**

This would have corresponded to **1,876 months** without the disease getting worse.

3.2 The case of pertuzumab in early breast cancer

Impact of earlier time to reimbursement for a therapy in the neo-adjuvant setting - the case of pertuzumab in early breast cancer, ***

Pertuzumab (pre-surgery or 'neoadjuvant')

Early stage breast cancer: the cancer is contained in the breast or it has only spread to the lymph nodes in the underarm area. In this stage, it is highly treatable, through a combination of surgery and treatment, and often radiation. Almost 90% of all patients diagnosed still live after five years.

Market Access: dates at which the therapy was reimbursed under a formal reimbursement scheme

2015				2016				2017				2018				2019			
Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4

Jul '15 **0** days | Dec '15 **126** days | Mar'16 **219** days | Nov '16 **478** days | Sep '19 **1496** days

EC Directive **180 days**

What if (scenarios) :

Gains versus standard-of-care:	## days between EC authorization and patient access:	'Ambitious' scenario A: Directly after EC authorization **0**			'Best practice' scenario B: As fast as the fastest country: **126**			'Basic' scenario C: Cf. EC Transparency Directive: **180**		
Country →		NL	SE	UK-ENG	NL	SE	UK-ENG	NL	SE	UK-ENG
	## additional patients treated →	339	147	1,695	n/a	42	1,138	n/a	26	1,056
LMG	## added months of life →	1,910	1,250	9,558	n/a	354	6,418	n/a	223	5,959
QALM	## added months of healthy life →	1,382	546	6,914	n/a	154	4,643	n/a	97	4,310

★★★★★ **In a highly ambitious scenario, if pertuzumab had been reimbursed in the Netherlands, Sweden and England directly after EC marketing approval:**

2,180 more patients with early breast cancer could have been treated.

They could have lived altogether an additional **12,718 months.**

This would have corresponded to **8,842 months** when adjusted for the quality of life.

★★★★☆ **In the 'best practice' scenario, if pertuzumab had been reimbursed in Sweden and England after 126 days, like in the Netherlands:**

1,180 more patients with early breast cancer could have been treated.

They could have lived altogether an additional **6,772 months.**

This would have corresponded to **4,798 months** when adjusted for the quality of life.

★★★☆☆ **In the 'basic scenario, if pertuzumab had been reimbursed in Sweden and England as fast as agreed in the EC Transparency Directive (a condition fulfilled by the Netherlands):**

1,083 more patients with early breast cancer could have been treated.

They could have lived altogether an additional **6,181 months.**

This would have corresponded to **4,408 months** when adjusted for the quality of life.

* The added months of life represent an average that includes patients who were cured and had no cancer recurrence.

** Pertuzumab for early breast cancer is not reimbursed in Italy and Portugal. In Poland it was only reimbursed as of September 2019, resulting in too little uptake information for inclusion in the analysis.

Box 2

Impact analysis of improved time to market access – summary of methodology

For the impact analysis, the number of new patients on the therapy (uptake) per month were retrieved from the routinely collected business information of the companies involved, as of the date of formal reimbursement. Subsequently, three hypothetical scenarios were applied. In these scenarios, the number of new patients per month remained equal. But time to reimbursement (start of uptake) changed.

- **Scenario A:** at the time of the EC marketing authorisation.
  In this 'highly ambitious' scenario, time to market access as short as possible. In this scenario, market access is achieved at the time of the European Commission's (EC) marketing authorisation.
- **Scenario B:** as fast as the fastest country.
  In this 'best practice' scenario, the potential gains are assessed for a situation in which all countries ensure market access as fast as the fastest country.
- **Scenario C:** at 180 days after the EC marketing authorisation.
  In this 'basic' scenario, dossiers are submitted directly after EC marketing authorisation and all stakeholders involved adhere to a timeline of max. 180 days to achieve market access, in conformity with the EC Transparency Directive (European Commission, 1988).

The scenarios were researched in all six case study countries. A health economic model was developed to calculate for each therapy and country the impact of the three scenarios on the number of patients that could have been treated, and the resulting health impact. This was done using three steps (more details are provided in Annex D):

1. Calculate the improvement in time to patient access: determine the difference in days between the optimised scenario and the actual scenario.
2. Calculate the additional number of patients that could have been treated if the uptake curve would have started at this new date (the endpoint for both uptake curves was set at five years).
3. Calculate the health gains per month based on the information in the country-specific reimbursement dossiers: multiply the number of patients with the incremental health gains per month, expressed in terms of overall survival (OS, per month), event-free survival (EFS, per month), life-years gained (LYG, translated into life-months gained, LMG) and/or quality-adjusted life years (QALYs, translated into quality-adjusted life-months, QALMs) gained versus the comparator.

4. The ten key factors delaying patient access

TEN reasons explain why many patients in European countries tend to have longer waiting times than needed to access new cancer medicines. These reasons are the result of the current systems in which stakeholders operate and can be categorized as factors related to:

- **Process, i.e. how stakeholders organize the series of steps to take**
  Three key process-related factors delaying patient access are: late start of application and submission, lack of adherence to maximum timelines and a multitude of layers involved in the decision-making process.
- **Reimbursement criteria, i.e. what information stakeholders use to define value**
  In this category, delays take place due to different evidence requirements across Europe and a lack of clarity of national assessment requirements. These are followed by gaps between evidence submitted and evidence required, and subsequent misalignment of views on value and price.
- **Health system readiness, i.e. to what extent stakeholders integrate the therapy in clinical practice**
  Once a positive reimbursement decision has been made, integration in clinical practice may be hampered due to prescriber's depleted budgets before the end of the fiscal period, a low frequency at which clinical guidelines are updated and the state of the healthcare infrastructure.

Each of these factors is described in detail in this chapter. Applying this comprehensive framework enables a constructive dialogue and the identification of joint solutions.

4.1 Late start of application and submission

The longer it takes to initiate the national access pathway for a new therapy, the later patients will actually have access to this new therapy.

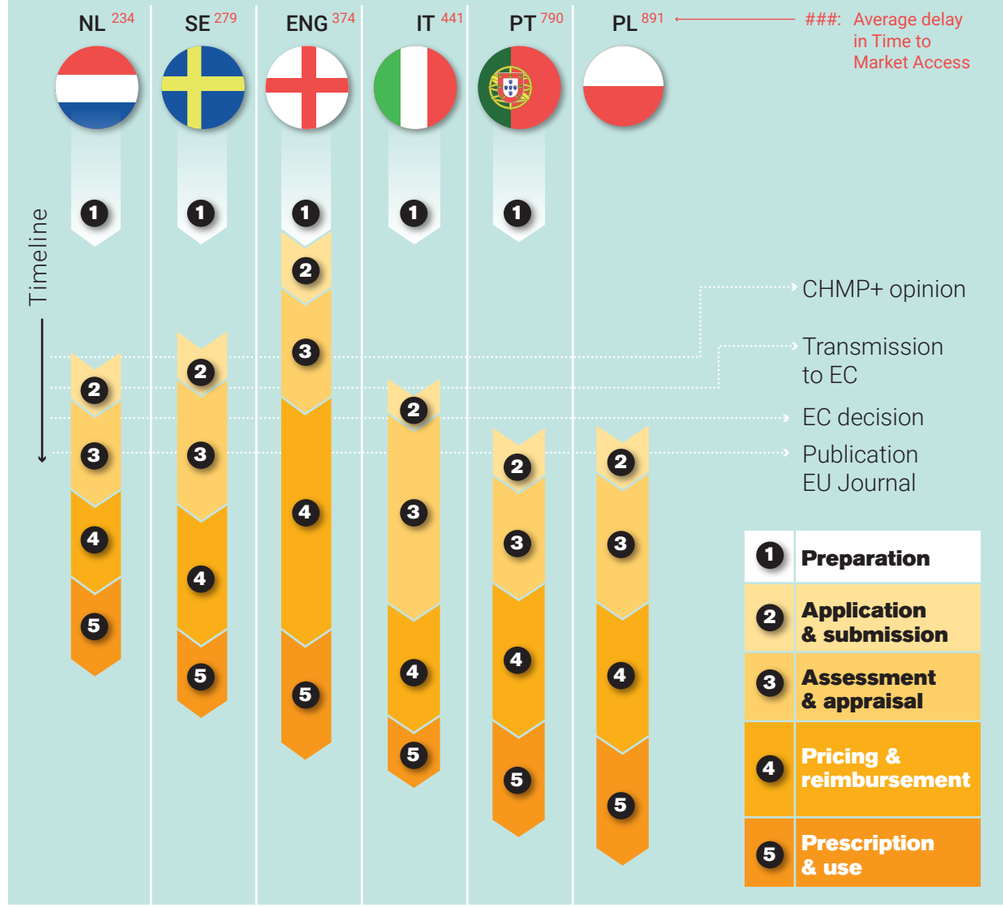
Often, countries await a positive opinion from the EMA Committee for Medicinal Products for Human Use (CHMP), or in some case the formal decision from the European Commission (EC)*, or the formal publication in the Official Journal of the EU before a dossier can be submitted or is assessed. In some cases, countries even await decisions from other countries (Yfantopoulos & Chantzaras, 2018).

Figure 7 shows how the moment of starting the process differs for the six case study countries.

Most European countries use External Reference Pricing (ERP) to manage and negotiate pharmaceutical prices. With ERP, medicine price(s) in one or more other countries serve as a benchmark or reference price for setting or negotiating the price in a country. Here, list prices are used rather than the net transaction prices, as the latter are generally confidential. The number of countries considered in the basket varies across countries, ranging from 3 to 30 countries. This is reflected in Figure 8. External Reference Pricing is used in Europe but European countries are also referenced by non-European countries (Holtorf, Gialama, Wijaya, & Kaló, 2019).

In some cases, higher-income countries reference lower-income countries. Consequently, establishing a reimbursement price in countries with a lower ability to pay and hence a lower price level first, before

Fig. 7
Start of the national process in the six case study countries

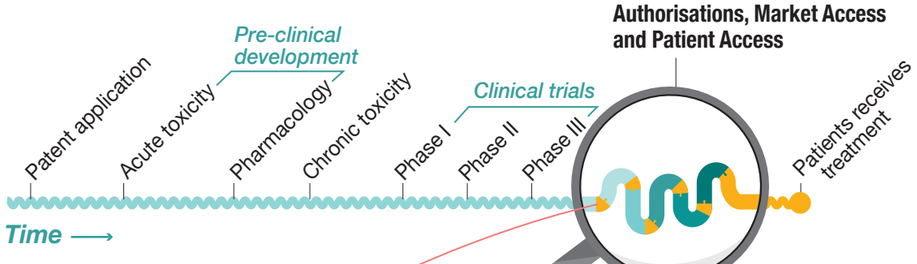


* Following a CHMP opinion the European Commission usually adopts a legally binding authorization, within 67 days.

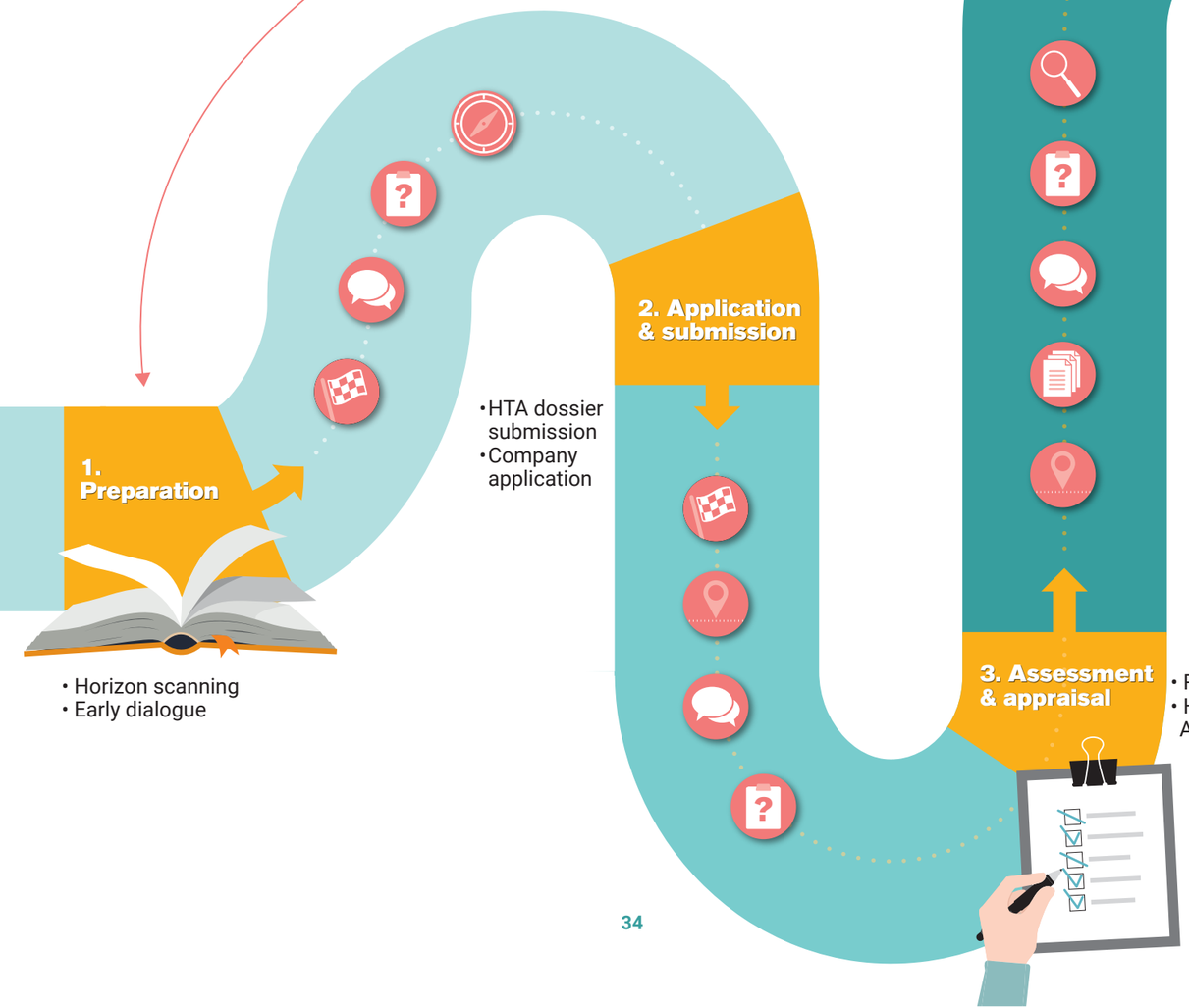
Every day counts

IMPROVING TIME TO PATIENT ACCESS TO INNOVATIVE ONCOLOGY THERAPIES IN EUROPE

The lifecycle of a medicine



This infographic shows the last milestones of the process: Authorisations, Market Access and Patient Access



The ten key factors delaying patient access

PROCESS

1. Late start
2. Undefined timelines
3. Multiple layers

REIMBURSEMENT CRITERIA

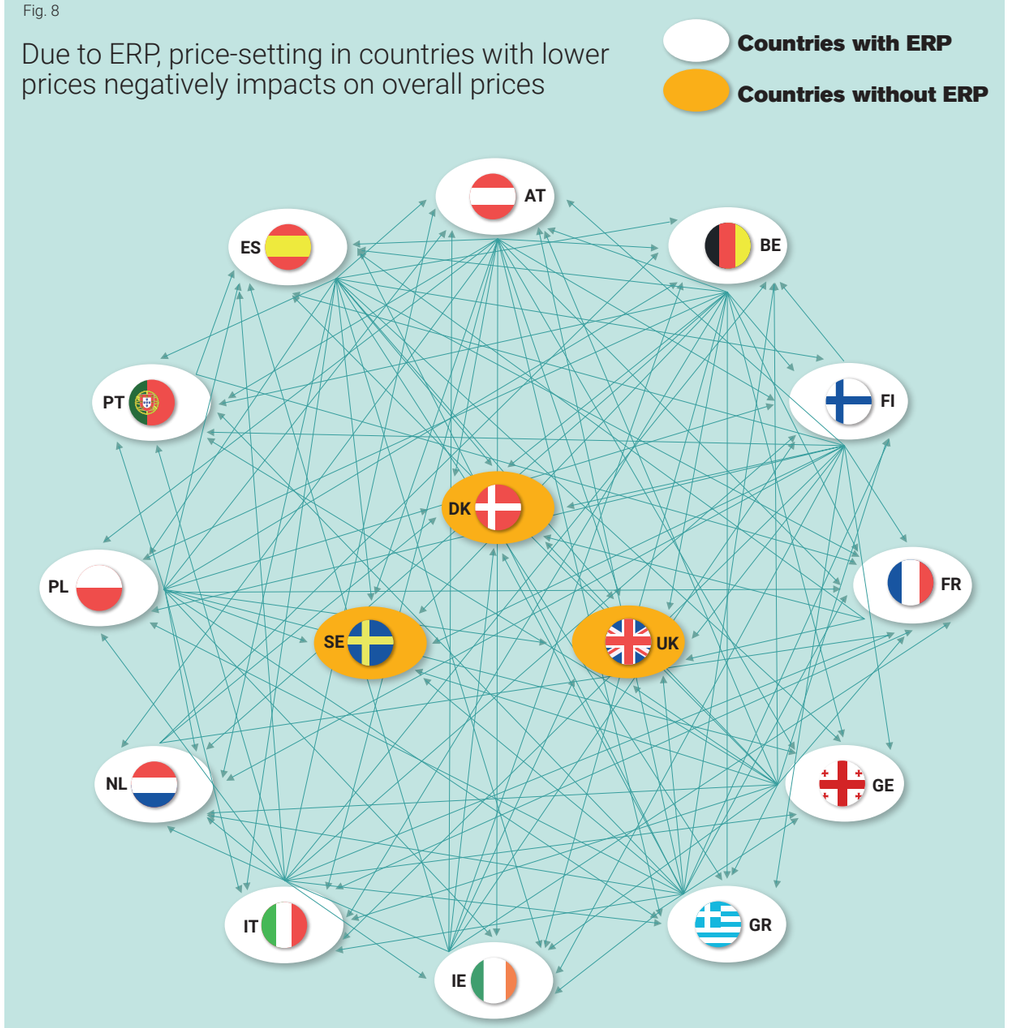
4. Different requirements
5. Lack of clarity
6. Evidence gaps
7. Misalignment on value and price

HEALTH SYSTEM READINESS

8. Budget restraints
9. Outdated clinical guidelines
10. Suboptimal healthcare infrastructure

Fig. 8

Due to ERP, price-setting in countries with lower prices negatively impacts on overall prices



Source: Panteli, et al., 2016

doing so in countries with higher ability to pay, will result in a general price decrease across European countries. This creates an incentive for companies to launch in high-income countries first (and hampers application of differential prices), to avoid lower prices cascading from one country to another (Kanavos, Fontrier, Gill, & Efthymiadou, 2020).

Another important factor at play behind these dynamics is the scarcity of human resources within both HTA bodies and pharmaceutical companies. Significant advances in medical science and deeper understanding of diseases have led to an acceleration of drug development in all disease areas. With the number of EU marketing authorizations increasing, even more capacity will be required. HTA bodies struggle to compete with private sector salaries and to ensure they have the required expertise in a rapidly advancing field (O'Rourke, Werkö, Merlin, Huang, & Schuller, 2019). For that reason, they

are often inclined not to accept an application for reimbursement until authorization to enter the European market has been confirmed. Similarly, companies (especially smaller and mid-sized companies) do not have the capacity to submit all national dossiers in parallel throughout Europe, as every single country requires the development of a tailor-made dossier in local language and compliance with a country-specific trajectory.

4.2 Lack of adherence to maximum timelines

Most European countries do not follow a clear set of rules around the timelines for decision-making on national pricing and reimbursement. Even when countries have such rules in place, compliance can be challenging.

This results in delays and unpredictability of timelines. In the case of the Netherlands for example, the average time between a European marketing authorization and a positive formal reimbursement decision is 234 days for oncology therapies. However, actual delays vary a lot between therapies and may take up to ~700 days in the case of the Netherlands (as shown in the WAIT indicator report), depending e.g. on whether or not the clock stop* procedure is used.

Recent evidence shows how delays in reimbursement of oncology therapies vary within countries, making the process unpredictable (IQVIA, 2020).* This reflects a suboptimal implementation of the EU Transparency Directive (European Commission, 1988). The purpose of this directive is to ensure the transparency of measures that regulate pricing and reimbursement of medicinal products. It sets the maximum duration for reaching a national pricing and reimbursement decision to a strict national timeline of max. 180 days. This timeline starts from the moment a dossier is submitted and excludes time needed by companies to provide additional information ('clock stops').

4.3 Multiple layers of decision-making

Figure 4 (section 2.2) summarizes how European countries have a different way of organizing their reimbursement decision-making process. The more levels of decision-making, the more duplication of efforts occurs and the higher the chances of prolonging the time before patients can access treatments.

- **Delays related to duplication of reimbursement decisions** take place in countries such as Italy and Sweden. Here, regions (or counties) can make their own reimbursement decision. In Italy, regions can conduct the assessment themselves.
- **Delays related to duplication of budget decisions** take place in countries such as the Netherlands and Portugal. After a positive reimbursement decision at national level, individual negotiations on net price and inclusion of therapies in the hospital formulary need to take place with the hospitals themselves.
- **Delays related to implementing budget decisions** are seen in Poland for example, where budget allocation to hospitals can be delayed by several months.

In addition, decentralized decision-making also increases the risk of inequalities in access within a country.

* It is important to note that timelines presented in this publication capture three delays which are excluded from the 180 days prescribed by the EU Transparency Directive. First, the delay between marketing authorization and dossier submission, since the 180 days start from the moment of dossier submission. Second, delays during the assessment due to 'clock stops', as the 180 days exclude time needed by companies to provide additional information. And third, delays due to putting formalities in place, as the Transparency Directive stops at the moment of the decision.

4.4 Different evidence requirements across Europe

Throughout Europe, different evidence is required for a **clinical assessment**, depending on the assessment agencies. Evidence required by the EMA to demonstrate safety and clinical efficacy and inform a marketing authorization decision differs from the evidence required by national HTA bodies to demonstrate clinical effectiveness and inform reimbursement decisions. This makes sense, as both agencies have different objectives.

Yet, even among HTA bodies, who all aim to answer similar evaluation questions, evidence requirements vary. When evaluating clinical effectiveness, HTA bodies look at the strength of the evidence generated by the manufacturer in a clinical trial. They assess whether the evidence is robust enough to demonstrate the effectiveness compared to existing alternatives (e.g. the current standard of care). They look at the patient population that was studied, the comparator therapy that was used, the clinical endpoints (outcomes) that were measured, the way in which the trial was set-up, and the statistical analyzes that were run.

However, the extent to which this evidence (coming from the same clinical trial) is considered robust or acceptable varies greatly across HTA bodies. This is demonstrated in Figure 9, which maps the self-reported level of acceptance of 19 trial characteristics for the HTA bodies in England, Italy, the Netherlands, Poland, Portugal and Sweden.

Fig. 9

Acceptance of evidence characteristics by EMA

and six national HTA bodies, based on self-assessment by agency representatives

Legend

Accepted | **Often accepted** | **Case-dependent** | **Often not accepted** | **Not accepted**

Evidence characteristics (for the clinical or cost effectiveness assessment)		**Autho-rization** EMA	**Health technology assesment** UK-ENG	IT	NL	PL	PT	SE	**Level of align-ment** among HTA bodies
Population	• Target population as authorized by EMA	[N/A]							50%
	• Use of biomarkers								100%
	• Extrapolation to other populations								33%
Comparator	• Selected comparator								100%
	• Class effects								33%
	• Indirect comparisons								50%
Clinical end points	• PFS as endpoint								50%
	• Other surrogate endpoints (non PFS)								0%
	• Absence of QoL data								50%
Trial design and data sources	• Real-world evidence								100%
	• Network Meta-Analysis								50%
	• Single armed trials								50%
	• Novel trial designs								50%
	• Cross over in trial								33%
	• Evidence from small population								67%
	• Short time period								50%
Statistical analysis	• Absence of statistical significance								67%
	• Post-hoc subgroup analyses								83%
	• Clinical relevance of effect acc. to EMA								67%
Level of acceptance per agency (HTA bodies and EMA)		**79%**	**68%**	**42%**	**47%**	**79%**	**37%**	**58%**	

Sources ASC Academics and Vintura, 2020 (see Annex C).

The level of alignment is highest for the use of biomarkers and real-world evidence (RWE) for example. These elements are "often accepted" by all HTA bodies. The level of alignment is lowest when HTA bodies are asked for acceptance of surrogate endpoints other than progression-free survival (PFS)*. Every agency looks at the use of surrogate endpoints other than OS or PFS in a different way: these are accepted in Poland and often accepted in Sweden; not accepted in the Netherlands and often not accepted in Portugal. England and Italy determine acceptance on a case-by-case basis.

These differences prolong discussions and alignment between pharmaceutical companies and HTA bodies at a national level, especially when no early discussions took place to align on evidence generation in advance. It may even lead to additional, country-specific data collection, thereby seriously extending patients' waiting times.

4.5 Lack of clarity of national requirements

In addition to a lack of coherence on evidence requirements between HTA bodies, also within countries the evidence requirements for the clinical assessment and the cost-effectiveness assessment are often difficult to predict. Although case-dependency allows for a tailor-made assessment, it also results in an unpredictable evaluation. The absence of clearly defined criteria and requirements, or their inconsistent application, perpetuates national discussions and misalignment between pharmaceutical companies and HTA bodies, thereby delaying access for patients.

Unclear evidence requirements for clinical assessments, within countries

Figure 10 demonstrates the difficulty of predicting evidence requirements for the clinical assessment with national HTA bodies.

In Figure 9, the grey color code reflects acceptance on a case-by-case basis. The blue color code ("often not accepted") and lighter orange color ("often accepted") also reflect a certain level of unpredictability. To highlight the level of predictability more clearly, in Figure 10 the information from Figure 9 is translated into levels of predictability, using the general rules**:

- 'accepted' and 'not accepted' are classified as 'predictable'
- 'often accepted' and 'often not accepted' are classified as 'not fully predictable'
- 'case-dependent' are classified as 'highly unpredictable'.

Mapping the information in this way shows how the level of predictability of evidence requirements is particularly low for the accepted patient population, the selected comparator, the use of PFS as an endpoint, cross-over in trials, a short time period of a trial (e.g. because of promising results and early, conditional marketing authorization) and post-hoc subgroup analyses.

Unclear criteria for cost-effectiveness assessments, within countries

Similarly, criteria for the cost-effectiveness assessment are not always defined in a clear manner, nor is the definition used in a

* As shown in the Table, also PFS as an endpoint is not always accepted, e.g. in Italy and Portugal.

** This was adapted when needed, e.g. in the case of acceptance of biomarkers or indirect comparisons which are often accepted ("accepted when validated" and "accepted when needed and done in accordance with guidelines" respectively), yet fully predictable.

Fig. 10

Predictability of evidence requirements from EMA

and six national HTA bodies, based on self-assessment by agency representatives

Legend

Highly unpredictable (Case-dependent)

Not fully predictable (Often accepted; Often not accepted)

Predictable (Accepted; Not accepted)

Evidence characteristics (for the clinical or cost effectiveness assessment)		**Autho-rization**	**Health technology assesment**						**Level of predicta-bility**
		EMA	UK-ENG	IT	NL	PL	PT	SE	across HTA bodies
Population	• Target population as authorized by EMA	[N/A]							17%
	• Use of biomarkers								100%
	• Extrapolation to other populations								17%
Comparator	• Selected comparator								0%
	• Class effects								50%
	• Indirect comparisons								100%
Clinical end points	• PFS as endpoint								17%
	• Other surrogate endpoints (non PFS)								33%
	• Absence of QoL data								50%
Trial design and data sources	• Real-world evidence								100%
	• Network Meta-Analysis								50%
	• Single armed trials								33%
	• Novel trial designs								33%
	• Cross-over in trial								17%
	• Evidence from small population								33%
	• Short time period								17%
Statistical analysis	• Absence of statistical significance								67%
	• Post-hoc subgroup analyses								17%
	• Clinical relevance of effect acc. to EMA								33%
Level of acceptance per agency (HTA bodies and EMA)		**68%**	**58%**	**32%**	**37%**	**53%**	**32%**	**37%**	

Sources ASC Academics and Vintura, 2020 (see Annex C.)

manner suitable for consistent application across situations. During a cost-effectiveness assessment, countries aim to answer the question: is price of the therapy a good reflection of its value? Countries apply different methodologies for determining cost-effectiveness, as shown in Figure 14.

HTA bodies in countries like England, the Netherlands and Poland apply a clear maximum price per quality-adjusted life year (QALY), also referred to as an incremental cost-effectiveness ratio (ICER). To a varying extent, they define different thresholds to allow applicability in different settings.

In England, specific thresholds are set for end-of-life settings and very rare diseases, to indicate a higher willingness to pay in these instances. In the Netherlands, willingness to pay is higher when the burden of the disease for patients is higher. These differences demonstrate the difficulty of defining and consistently applying clear thresholds in specific situations. In most countries, thresholds have not changed for many years (in some cases they have never been adjusted).

Fig. 11

Countries apply different methodologies for determining cost-effectiveness

Even when clear thresholds are defined, they are often not suitable for consistent application across situations

COUNTRY	**PRICE LEVEL CRITERIA**	**DETAILS**	**THRESHOLD**
UK-ENG	Maximum ICER (price / QALY)	• A general ICER threshold is applied. • A higher threshold is applied for (i) innovations delivering life extension in the later stages of terminal diseases and (ii) innovations targeting very rare diseases.	• General: £20k - £30k per QALY • End-of-life: £50k per QALY • Very rare diseases: £100k - £300k per QALY
IT	No clear criterium	• Pricing is done based on the degree of therapeutic innovation, the price of similar products within the same or similar therapeutic category, and product prices in other EU Member States.	• N/A
NL	Maximum ICER (price / QALY)	• Three different ICER thresholds are applied, depending on the disease burden being addressed. The disease burden ranges from 0,0 (no loss of future life years or quality of life) to 1,0 (complete loss of future life years and quality of life).	• Disease burden 0,1 – 0,4: €20k per QALY • Disease burden 0,41 – 0,7: €50k per QALY • Disease burden 0,71 – 1,0: €80k per QALY
PL	Maximum ICER (price / QALY)	• A general ICER threshold is applied. All medicines (incl. orphan drugs) must meet a strict ICER threshold of €40,485/QALY, which represents three times the GDP per capita. • A current late-stage initiative intends to allow for a less strict ICER threshold for orphan drugs.	• €40k per QALY
PT	No clear criterium	• Pricing is done based on the level of innovation and economic advantage compared to existing therapies and product prices in 3 reference countries.	• N/A
SE	No clear criterium	• TLV conducts the economic assessments of pharmaceuticals used in the specialized in-patient care and provides a report which includes a health economic	• N/A

Sources Nanavaty, et al., 2015; Paulden, 2017; Zorginstituut Nederland, 2018

Other European countries do not define clear thresholds at all.

In Sweden, the HTA body assesses the price per QALY at different price levels but does not use a standard maximum price to reflect what is considered a reasonable price per QALY (Svensson, Nilsson, & Arnberg, 2015). Countries like Italy or Portugal also do not have a formal ICER threshold. In order to decide on an acceptable price, they compare the price of a new therapy to prices of similar therapies and/or prices in other countries (Iannazzo, et al., 2016). The differences are summarized Figure 11.

4.6 Evidence gaps

Increasingly, reimbursement dossiers for oncology therapies risk not meeting evidence requirements from HTA bodies, leading to evidence gaps and uncertainty about the real-world value of these therapies. This can be due to non-robust evidence generation, but also due to the fact that meeting traditional HTA evidence requirements is getting more difficult given the characteristics of today's oncology therapies. This is especially the case when oncology therapies are:

Table 1

How oncology therapies inherently bring challenges in meeting evidence requirements for the clinical assessment, leading to gaps and uncertainty

THERAPY CHARACTERISTIC	CLINICAL TRIAL CHARACTERISTIC	UNCERTAINTY
Therapy-characteristic	• Selected comparator: The standard of care at the start of the trial has already been replaced at the time of evidence submission.	Uncertainty about effectiveness compared to country's standard of care.
Targeting life-threatening or highly debilitating disease	• Single-arm trial: The absence of alternative treatment makes it unethical to use a control group of patients not receiving the potentially effective therapy. • Cross-over in trial: The absence of alternative treatment makes it unethical to keep patients in the control arm when their disease progresses. • Short time period: The promising effect makes it unethical to await all phases of the clinical trial before applying for marketing authorisation and reimbursement, meaning that 'hard' data on overall survival may not be available at the time of reimbursement discussions.	Uncertainty about validity of findings. Uncertainty about the relation between the observed effect and mortality or morbidity.
Targeting rare cancers (orphan drugs), molecular targets, or genomic alterations (targeted therapies and tumor-agnostic therapies)	• Evidence from small populations: As the disease, targeted molecule, or genomic alteration is rare, there are too few patients for: • having information on natural course of disease as comparison • developing a validated questionnaire to measure the effect • measuring a statistically significant effect size • Post-hoc subgroup analysis: The targeted effect does not occur in all patients, but it is not known (yet) in which patients exactly, making it impossible to predict in advance, in what subgroup the targeted effect will take place.	Uncertainty about statistical significance of findings.
Targeting cancers that progress slowly or have a long-term, curative effect	• Short time period: due to the slow progression of the disease, no 'hard' data on overall survival may be available within a reasonable timeframe, or no evidence on the actual duration of the (potential) curative effect may be available within a reasonable timeframe.	Uncertainty about the relation between the observed effect and mortality or morbidity. Uncertainty about the long-term duration of the effect.

- generally developed in a context with a high speed of innovation
- often targeting life-threatening or highly debilitating disease
- frequently targeting rare cancers, molecular targets, or genomic alterations
- sometimes targeting cancers that progress slowly (especially when targeting the cancer at an early stage when there is more potential to significantly prolong life expectancy)
- sometimes able to cure.

Table 1 describes how these characteristics result in clinical trial designs not meeting national evidence requirements for the clinical assessment. Consequently, they bring evidence gaps and uncertainty about real-world value.

This is complicated further by the fact that these therapies also pose challenges to determining cost-effectiveness. In the case of some multi-indication therapies or *tumor-agnostic therapies* for example, the same therapy is used for different types of tumors. This poses the difficulty of applying different value assessments per indication and indication-specific prices (the latter is often hampered by the way in which information on prescription is collected at the hospital level). In the case of therapies with a curative intent, the uncertainty about the duration of the effect is of particular consequence due to the upfront payment that has to be made for this one-off therapy.

4.7 Misalignment on value and price

Decision-makers are faced with the enormous challenge of striking a balance between fast patient access, uncertainty about real-world value, and a reasonable price reflecting the (potential) value. They have to do this in the context of assessment criteria and evidence requirements that are not black-and-white and amid different views from pharmaceutical companies and the decision-makers on value and affordability.

As described in the previous sections, the evidence submitted may contain gaps compared to evidence requirements. This could be due to evidence requirements being different across Europe (section 4.4), being unpredictable within countries (section 4.5), being incompatible with the therapy characteristics, or because pharmaceutical companies underestimate the information need (section 4.6).

Whatever their cause, these evidence gaps are the source of a vicious circle:

Misalignment on value and price: pharmaceutical companies and decision-makers have difficulty in achieving a shared perspective on the value of the therapy: does it have a high added value, or does it have a highly uncertain effect? Misalignment on value hampers alignment on price: is the price reflective of an appropriate return for value and risk, or does it pose an unjustified budget risk in the absence of certainty about the real-world effect?

Long negotiations and decreasing trust: consequently, long negotiations take place that focus merely on price in the absence of mechanisms to deal with the uncertainty about value. In these price negotiations, the common ground is often simply lost. Pharmaceutical companies and decision-makers find themselves in opposing positions on price, without room for a constructive, comprehensive dialogue focused to find a shared solution.

This lack of trust is adding to the strain on the relationship between healthcare stakeholders and their growing disconnect, caused by:

- Increasing pressure on healthcare budgets, due to aging populations, higher incidence

of chronic diseases and the rapid evolution of therapeutic options, targeting smaller populations (implying higher list prices per patient).
- (Perceived) asymmetry of information due to lack of insights in costs involved in research and development of a therapy.
- Examples of bad decisions by individual companies and instances of negative media exposure and framing.

Subsequently, during new reimbursement trajectories, there is less trust when value and price are being discussed.

4.8 Insufficient budget to implement decisions

Once a reimbursement decision has been made, there are still factors that can delay the time to patient access. One of these factors includes ensuring enough budget is available to implement the decision in practice, and/or to fund the medicine for the remainder of the financial year. When an insufficient budget is in place, this delays access or hampers access by putting negative pressure on the prescription and use of the new medication.

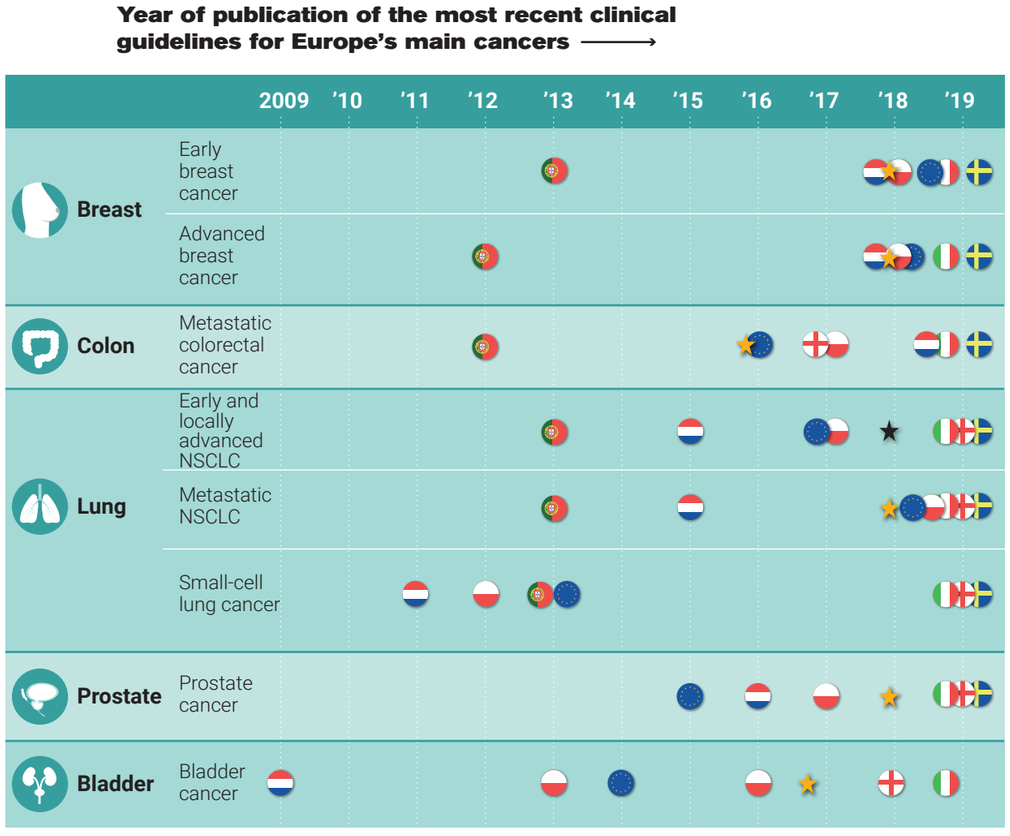
In England for example, although the National Health Service (NHS) is required to fund reimbursement recommendations from the National Institute for Health and Care Excellence (NICE) nationally through NHS England and locally through Clinical Commissioning Groups (CCGs), in practice "postcode prescribing" (geographical variation in access) occurs because of local budget constraints (Edwards, Appleby, & Timmins, 2019).

In the Netherlands, the same "postcode prescribing" may occur when prescribers need to refer patients to other care centers because of "selective purchasing" (healthcare insurers reimburse certain medicines only when prescribed in specific hospitals), or because a reimbursement cap set by healthcare insurers is reached (NZa, 2019).

In Poland, new patient enrolment in the Drug Program may be delayed because of budget depletion for the ongoing budget period.

Fig. 12

Clinical guidelines do not always include the most recent therapeutic innovations
Even for Europe's 5 main cancer types



Source NICE, 2020, Associazione Italiana di Oncologia Medica, 2020, Integraal Kankercentrum Nederland, 2020, Serviço Nacional de Saúde , 2020, Regionala Cancercertrum, 2020, European Society for Medical Oncology, 2020.

4.9 Low frequency of clinical guideline updates

As shown in Figure 12, clinical guidelines do not always include the most recent therapeutic innovations, even for Europe's five main cancer types (WHO International Agency for Research on Cancer, 2020). The absence of clinical guidelines may cause prescribers to hold back from starting to use new therapies due to a lack of clarity on the positioning of the new therapy in the treatment pathway. Pharmaceutical companies have an important role to play in developing the required body of evidence and creating awareness to inform clinical guidelines.

4.10 Suboptimal healthcare infrastructure

The health infrastructure faces constraints in many European countries, leading to a suboptimal organization of oncology pathways. For that reason, even after reimbursement, healthcare systems may face difficulties absorbing and using a new therapy in the most optimal way. As basic conditions, patients need to have access to high quality health facilities, diagnostic centres and health personnel. More specifically, the oncology care pathway should facilitate the optimal use of innovative therapies through:

- **Screening:** focus on early detection and the use of the growing evidence on risk factors (e.g. inherited genetic mutations).
- **Diagnosis:** the availability of rapid diagnostic centers and reimbursement of appropriate (genetic/biomarker) testing methods.
- **Referral and treatment:** timely access to centers of excellence specialized in (rare) cancers, access to the latest information on accessibility of innovative oncology therapies, and absence of financial considerations with prescribers and patients when selecting a therapy.
- **Follow-up:** optimal adherence to (chronic and/or extramural) treatment regimens and monitoring of investments and (patient-relevant) outcomes to inform future prescriptions.

5. The six priority areas for reducing the time to patient access

THERE are six priority areas to address the ten factors causing delays in patient access. In each of these priority areas, a concerted effort is needed. It is not a matter of individual stakeholders taking responsibility within their respective areas of work. It requires stakeholders to break through comfort zones and to actively look for common ground with other stakeholders.

The six priority areas shown in Table 2 serve as a starting point for a further and constructive dialogues and joint problem-solving.

Each of these areas are described in more detail below. After a short description, recommendations for tangible next steps are exemplified using best practices that already exist. Together, these priority areas for action address all ten factors causing cancer patients in Europe to wait longer to get access to new cancer medicines.

Table 2

Category	#	Priority area
PROCESS	1	Align dossier submission timelines
	2	Shorten reimbursement timelines
REIMBURSEMENT CRITERIA	3	Align evidence requirements
	4	Be adaptive to rapidly evolving innovation
HEALTH SYSTEM READINESS	5	Improve healthcare infrastructures
	6	Strengthen collaboration between all stakeholders

5.1 Align dossier submission timelines

Almost all European countries apply external reference pricing, i.e. set maximum prices based on the prices of other countries. In some cases, higher-income countries reference lower-income countries, creating an incentive for companies to launch in high-income countries first (Kanavos, Fontrier, Gill, & Efthymiadou, 2020). As a result, external reference pricing leads to countries with a lower ability to pay waiting much longer for the introduction of new medications.

This is partly mitigated through highly confidential discounts which allow for differential pricing without impacting on list prices that are used for ERP. However, a negative side effect is that a lack of transparency on actual prices increases mistrust with stakeholders who were not involved in the national pricing and reimbursement discussions.

If countries could address external reference pricing and its unintended consequences, the need for later introduction in countries with a lower ability to pay and confidential discounts would be greatly reduced. This would facilitate earlier submission in these countries, whilst increasing transparency and trust in the system at the same time.

To realize this, stakeholders ought to evaluate current strategies and their impact on dossier submission timelines and explore improvements or alternatives. An alternative could e.g. be a European solidarity system, wherein prices are differentiated explicitly, based on a single reference price and objective and previously agreed parameters reflecting the economic situation of a country. This should be accompanied by efforts to reduce differences in healthcare expenditures by countries that currently spend less on healthcare compared to the European average, to avoid erosion of this solidarity system. An aspect to consider is the cross-border trade of oncology medicines that may follow from important price differences between countries. And finally, also HTA capacity within pharmaceutical companies should allow for parallel dossier submission across European countries once the bottleneck of ERP is addressed.

Delaying factor(s) addressed

- (#1) Late start of application and submission, due to external reference pricing.

Align dossier submission timelines - recommended next steps

Stakeholders	Next steps
National authorities & Multi-stakeholder collaborations	Evaluate the advantages and disadvantages of current ERP strategies and explore improvements or alternatives.
Academics and experts	Identify alternative solutions for ERP, e.g. based on explicit differential pricing (solidarity) and smaller differences in healthcare expenditures.
Pharmaceutical companies	Build HTA capabilities to allow for more dossier submissions in parallel across European countries once ERP as a bottleneck is addressed.

Best practices

The United Kingdom, Denmark and Sweden do not apply external reference pricing to determine and negotiate prices (Panteli, et al., 2016).

Kanavos et al. evaluated the impact of ERP on key health policy objectives in different national contexts. They concluded ERP has not regulated prices efficiently and has unintended consequences that reduce benefits arising from it (Kanavos, Fontrier, Gill, & Efthymiadou, 2020).

Poland decided to increase healthcare spending as % of GDP with 25% by 2024, thereby reducing differences in healthcare expenditures between European countries, an important prerequisite in the case of a differential pricing system based on solidarity (Sowada, Sagan, & Kowalska-Bobko, 2019).

5.2 Shorten reimbursement timelines

In the preparation phase, early dialogues, horizon scanning and early collaboration allow for optimal preparation already prior to European marketing authorization. Pre-alignment in this stage provides a great opportunity for quicker alignment during the subsequent phases (e.g. on requirements, evidence gaps, value and price).

Dossier submission could start earlier than the moment a European marketing authorization is formally granted. It could also start much earlier by avoiding waiting for decisions from other countries. During the process, steps could be taken in parallel instead of sequentially and the layers of decision-making could be reduced to a minimum to reduce time to patient access. This requires enough HTA capacity within HTA bodies.

A key challenge of the medicine reimbursement process is that the traditional provider-consumer transaction is distorted. The patient as the consumer of the final product is represented by collective payer institutions. As a result, the patient perspective is easily replaced by an administrative and financial dialogue. The demand for urgency is not structurally included in the process. Informed patients should be engaged in every step of the decision-making process, as a continuous reminder to all stakeholders that for patients, every day counts. Last but not least, making timelines transparent helps in maintaining a sense of urgency at every step of the process.

There are many opportunities to improve reimbursement timelines and countries can learn a lot from other countries. In Germany for example, an access pathway is used whereby therapies are reimbursed directly after marketing authorization, prior to the HTA, based on list prices set by pharmaceutical companies. Within six months, an HTA is conducted, after which the actual reimbursement price is negotiated. This price replaces the initial price one year after launch. In England, dossiers can be submitted prior to a positive CHMP opinion, to allow for taking as many steps in the process in advance.

Delaying factor(s) addressed

- (#1) Late start of application and submission, due to national timelines
- (#2) Lack of adherence to maximum timelines
- (#3) Multiple layers of decision-making

In particular by preparing well in advance of EU marketing authorization, delays due to the following factors can be addressed:

- (#4) Different evidence requirements across Europe
- (#5) Lack of clarity of national requirements
- (#6) Evidence gaps
- (#7) Misalignment on value and price

Shorten reimbursement timelines - recommended next steps

Stakeholders	Next steps
National authorities	Evaluate the access pathway from a process-optimisation perspective and identify opportunities to shorten timelines.
	Build HTA capabilities.
	Involve informed patients to maintain a sense of urgency at every step of the access pathway.
Pharmaceutical companies	Have the dossier ready in time and submit as soon as national timelines permit.
Patient organisations	Educate and support authorities regarding the engagement of informed patients at every step of the access pathway.

Best practices

In **Germany**, patient access is granted prior to HTA, at the time of EU marketing authorization. After authorization, companies set their list price and submit their dossier to the Joint Federal Committee (G-BA). Within six months, G-BA assesses the added benefit, after which the reimbursement price is negotiated. This price replaces the initial price one year after launch (OECD, 2018).

In the **Netherlands**, a pilot is ongoing to evaluate a parallel instead of sequential procedure for authorization and reimbursement (Zorginstituut Nederland, 2019).

In **Belgium, Denmark, and the Netherlands**, multi-year, multi-indication agreements include light-touch or no assessments for new indications, and the price and impact on budget of new indications are discussed at the beginning of the agreement (Wilson, Voncina, Breen, & Roediger).

In **England**, NICE proactively invites manufacturers to submit their dossiers before a positive CHMP opinion is in place. Assessment timelines are published on the NICE website (NICE, 2018). All decisions are made at the central level and will also be recognized in Wales. For positive reimbursement decisions the NHS is obliged to ensure budget for local implementation (Edwards, Appleby, & Timmins, 2019). For cancer drugs that are recommended for use within the Cancer Drugs Fund (CDF), the NICE appraisal process starts much earlier with the aim of publishing draft guidance prior to a drug receiving its marketing authorization and then final guidance within 90 days of marketing authorization (NHS England, 2016).

Italy's fund for innovative oncology drugs enables faster patient access by removing budgetary barriers at the regional level (Flume, et al., 2018).

The **European Patients' Academy (EUPATI)** has launched a training course for academia and industry professionals on the principles of good patient engagement and helps participants plan for including the right patients at the right time for the right purpose. In this way, EUPATI supports engagement of informed patients and strengthening a sense of urgency at every step of the access pathway (EUPATI, 2020).

5.3 Align evidence requirements

Much like the EMA has improved the efficiency for granting market authorizations, European HTA alignment on clinical assessment (after which appraisal takes place at the national level) would improve the timelines to patient access. In addition, European cooperation and alignment would reduce duplication of efforts and allow for more efficient use of scarce human and financial resources (Huic, 2016). The European Network for Health Technology Assessment (EUnetHTA) started in 2009 following a call from the European Commission. It has become the network for HTA collaboration across Europe and joint clinical assessments (JCAs). It has been put in place until 2021 and currently works on establishing a permanent HTA working structure for Europe, with a focus on the clinical assessment. In follow-up to EUnetHTA, in 2018 the European Commission published a Proposal for a Regulation on Health Technology Assessment, to formalize European collaboration further and introduce Joint Clinical Assessments (European Commission, 2018). The Proposal has since been extensively discussed but divergent positions remain (Vella Bonanno, et al., 2019).

However, given the serious delays caused by differences in evidence requirements in the various European jurisdictions, all stakeholders should contribute to approval of a fit-for-purpose EC Regulation on HTA. At the very least, countries should exchange their views on requirements and assessment methodologies, particularly for new generations of medicines.

Delaying factor(s) addressed

- (#4) Different evidence requirements across Europe
- (#5) Lack of clarity of national requirements (clinical assessment)

Best practices

Since 1995, single European marketing authorizations are granted based on an opinion from **EMA** and a legally binding decision from the **European Commission** (EMA, 2020).

EUnetHTA facilitates HTA collaboration across Europe and joint clinical assessments (EUnetHTA, 2020).

The **European Commission** Proposal for a Regulation on Health Technology Assessment aims to formalize European collaboration further and introduce JCAs after the expiry of EUnetHTA's mandate (European Commission, 2018).

To help generate optimal and robust evidence that satisfies the needs of both regulators and HTA bodies, **EMA** and **EUnetHTA** offer joint scientific advice on development programmes (Tafuri, et al., 2016).

Since its start, **pharmaceutical companies** have submitted seven oncology therapies through EUnetHTA (Joint Action 1, 2 and 3), thereby contributing to the strengthening of joint clinical assessments in Europe: pazopanib, sorafenib, ramucirumab, midostaurin, regorafenib, alectinib and the combination of polatuzumab vedotin, bendamustine and rituximab (EUnetHTA, 2020).

Align evidence requirements - recommended next steps

Stakeholders	Next steps
National authorities	Politically support joint clinical assessments and approval of a fit-for-purpose EC Regulation on HTA.
HTA bodies	Internationally exchange and create consensus on requirements and assessment methodologies.
Pharmaceutical companies	Submit pharmacotherapeutic dossiers through EUnetHTA or a future European HTA coordination mechanism. Design trials which fit the joint requirements.

Table 3

Example of reimbursement criteria in France

Category	Level of actual benefit	Price level
ASMR V	No improvement	Lower price/overall cost than comparators.
ASMR IV	Minor improvement	Parity price (for same population) or higher (for more restricted population).
ASMR III	Moderate improvement	Faster access (price notification instead of negotiation) and price consistency with rest of Europe.
ASMR II	Important improvement	
ASMR I	Major improvement	

5.4 Be adaptive to rapidly evolving innovation

All countries struggle with the same questions: how to define and assess value? How to manage uncertainty about the real-world value of therapies with high prices and/or high budget impact? How to assess cost-effectiveness of tumor-agnostic therapies and combination therapies? And how to manage the budget impact of one-off, curative therapies? These questions need to be answered in advance, to prevent delays when a new generation of therapies is brought forward for reimbursement.

Clear criteria reflecting society's definition of value

Reimbursement criteria need to be clear to allow for predictability, while at the same they should be flexible to enable applicability to a variety of therapies and cases.

The 'value-informed and affordable' pricing model provides an example of clear, yet flexible set of reimbursement criteria. It makes explicit which criteria influence decision-making and how. In this case, the theoretical model departs from the concept of 'value-based' pricing (as opposed to 'cost-based' pricing) and the aspects of disease severity and affordability are added. Cost-effectiveness thresholds are applied based on these dimensions: what does the payer consider good value for money for this disease severity, and given the size of the patient population (budget impact)? By allowing for cost-effectiveness thresholds that differ depending on disease severity and budget impact, the model makes explicit a higher societal willingness to pay in the case of a higher disease burden to patients and/or a small patient population and lower overall budget impact (Annemans, 2019).

The assessment framework used in France provides another example of clear reimbursement criteria. The framework also departs from 'value-based' pricing, with value being defined as the actual benefit compared to the standard of care (*l'amélioration de service médical rendu*, ASMR).

This is measured based on:

- Severity of the disease and its impact on morbidity and mortality
- Clinical efficacy/effectiveness and safety of the therapy
- Aim of the therapy: preventive, symptomatic or curative
- Therapeutic alternatives
- Impact on public health

Assessment against these criteria allows for determining the level of actual benefit, and thereby the appropriate price level (see Table 3).

A comprehensive system to manage uncertainties

Once reimbursement and assessment criteria are clear, the next challenge is to deal with uncertainty about the real-world value of therapies, due to evidence gaps that are increasingly inherent to today's oncology therapies.

A comprehensive system of horizon scanning, early collaboration, managed access schemes, and RWD generation should be in place to proactively manage today's challenges and avoid delays arising from them (see Figure 13).

Although European countries currently have different levels of implementing the four elements above, no comprehensive systems exist yet, in which:

1. **Horizon scanning** is used to identify and prepare for challenges related to assessment, reimbursement, and use after reimbursement.
2. **Early collaboration** supersedes today's early dialogue, symbolizing a move from early scientific advice towards broader discussions between stakeholders prior to EU marketing authorization, with the aim of aligning on challenges and jointly finding solutions (e.g. managed access scheme, novel payment models).
3. **Managed access schemes** allow for addressing access barriers and finding an optimal balance between uncertainty, price and fast access (e.g. fast track, conditional approval, novel payment models).
4. **Real-world data** is collected in a harmonized way, to develop evidence of real-world value (and costs) in a structured and comprehensive way to allow for closing of evidence gaps and novel payment models such as outcome-based agreements.

Novel payment models include innovative financial agreements to spread costs over time, allowing payers to control budget impact over the long term (in the case of high upfront costs for therapies with curative intent, as described in section 4.6). Additionally, outcome-based agreements, such as paying for results or value, can manage uncertainty and share risks related to real-world value (Ventura, 2019). While the actual system differs in each country, all countries should work towards a new, dynamic system.

Delaying factor(s) addressed

- (#5) Lack of clarity of national requirements (clinical- and cost-effectiveness assessment)
- (#6) Evidence gaps

Fig. 13

Comprehensive system to manage uncertainty

	❶ Preparation	❷ A&S	❸ A&A	❹ P&R	❺ Prescription & use
Elements	**Horizon scanning** +	**Early collaboration** +	**Managed access schemes** +	**Real-world data**	
Description	Examination of the pipeline to flag issues for HTA capacity, assessment or health system readiness	Constructive early interaction between companies and agencies to discuss potential issues	Managed access schemes to address barriers, e.g. fast track, conditional approval, novel pricing methods	Monitor investments and outcomes in a structured and comprehensive way	
Result of these elements	Identify issues & prepare resources (e.g. capacity, expertise, budget)	Align on issues and solutions (e.g. adaptive pathway, innovative pricing)	Allow for optimal balance between uncertainty, price and fast access	Collect real-world evidence to close evidence gaps	
Maturity levels	**Flag**				
	Flag + discuss				
	Flag + discuss + address				
	Flag + discuss + address + monitor				

Allows for outcomes-based agreements

Be adaptive to rapidly evolving innovation - recommended next steps

Stakeholders	Next steps
National authorities	Collaborate to define clear joint reimbursement criteria. Make real-world data (RWD) collection integral to the introduction of new innovations.
Regulators, HTA bodies and payers	Develop a comprehensive system of horizon scanning, early collaboration, managed access schemes, and RWD generation to be ready for novel therapies.
Multi-stakeholder collaborations	Harmonise and align the collection of RWD.
Pharmaceutical companies	Prepare strong evidence-generation plans for effective early collaborations. Prepare well-substantiated pricing and financing proposals that address payer concerns.
Academics and experts	Support the development of clear reimbursement criteria.
Patient organisations	Generate and publish real-world, patient-generated data.

Best practices

In **Sweden**, a working group specifies the HTA methodology for e.g. CAR-T therapies. Another initiative aims to harmonize and expand patient registries to collect patient outcome data.

In **Poland**, an ongoing initiative aims to differentiate HTA/Reimbursement criteria for orphan from other innovative drugs, allowing for more flexible ICER and more transparency of decision-making criteria.

Since 2016, **NHS England's** Cancer Drugs Fund (CDF) allows for reimbursement of oncology therapies for which clinical uncertainties exist at the time of reimbursement discussions. This allows for evidence gaps to be closed during interim funding from CDF, until permanent reimbursement can be granted (NHS England, 2016).

In the **Netherlands**, the Drug Rediscovery Protocol (DRUP) provides an alternative data generation and reimbursement pathway for oncology precision drugs targeting small populations. In small cohorts, evidence is gathered to identify activity for off-label therapies. When activity has been demonstrated, outcome-based reimbursement is put in place (Van der Velden, et al., 2019).

The **Belgian** payer INAMI/RIZIV initiated the "Tool for Reducing Uncertainties in the evidence generation for Specialized Treatments for Rare Diseases" (TRUST-4RD) concept on the potential of RWE to close evidentiary gaps for HTA/payer decisions. Key in this concept is an early dialogue and collaboration to determine together the (real-world) evidence needed before and after reimbursement (TRUST-4RD, 2018).

The **International Consortium for Health Outcome Measurement (ICHOM)** develops standard sets of outcomes that matter most to patients. These sets cover five main cancer types, thereby providing a basis for harmonized and aligned real-world data collection (ICHOM, 2020).

The **Innovative Medicines Initiative** supports projects such as the European Health Data and Evidence Network (EHDEN), GetReal and Big Data for Better Outcomes (BD4BO) that support the transition towards more outcomes-focused and sustainable healthcare systems in Europe, making optimal use of real-world data (IMI, 2020).

5.5 Improve healthcare infrastructures

Even after reimbursement, patient access is not a given. Outdated guidelines prevent the adoption of innovations into practice, as do budgets when not aligned with reimbursement decisions.

Pricing and reimbursement decisions should lead to an update of the guidelines. A direct and continuous update of guidelines would be ideal, but an annual update should be considered a minimum. Given the high speed of innovation in oncology, these guidelines are an important tool to inform oncologists of new developments, especially in peripheral settings.

Similarly, pricing and reimbursement decisions should be reflected in (updated) budget provisions to ensure budget for immediate implementation and until the end of the financial year. Much of the information on delays in patient access due to budget scarcity or preliminary budget depletion is anecdotal, suggesting that these potential barriers and their impact on patient access should be monitored more closely.

To improve screening and diagnosis, clear roles and responsibilities need to be assigned. Whilst this sounds obvious, in practice limited accountability limits optimal screening and diagnosis. Furthermore, patients (especially with rare diseases) often do not have access to centres with the required specific expertise. Assigning clear centres of excellence for (rare) cancers and ensuring their accessibility (e.g. using e-health solutions) is key.

Improve healthcare infrastructures - recommended next steps

Stakeholders	Next steps
Professional associations	Define a streamlined process to allow for regular updates of clinical guidelines and ensure the resources required.
Patient organisations	Monitor the impact of budget scarcity/depletion on patient access.
Payers	Identify centres of excellence and ensure optimal accessibility of expertise.
National authorities	Appoint an authority for improving screening and diagnosis.
Pharmaceutical companies	Ensure robust clinical data to enable decisions on inclusion in the guidelines. Take payer concerns into account when developing price proposals.

Delaying factor(s) addressed

- (#8) Low frequency of clinical guideline updates
- (#9) Insufficient budget to implement decisions
- (#10) Suboptimal healthcare infrastructure

Best practices

In the **United States**, the National Comprehensive Cancer Network (NCCN) allows companies to submit a request for review of data for a specific indication, either before or after approval from the Food and Drug Administration (FDA).

In **England**, NICE developed interactive flowcharts comprising the content of both the latest clinical guidelines as well as additional treatment information based on recent technology appraisals.

In **Italy**, clinical guidelines are updated on an annual basis. Likewise, in Sweden, a Regional Cancer Centre developed guidelines for close to 40 cancer diseases/conditions that are updated on an annual basis.

The International Horizon Scanning Initiative (IHSI) is a collaboration of Belgium, Denmark, Ireland, the Netherlands, Norway, Portugal, Sweden and Switzerland that started in October 2019. The joint horizon scan should provide insight into which new innovations and products are reaching the market, thereby enabling decision-makers to effectively manage budgetary resources ahead of time (International Horizon Scanning Initiative, 2020).

In **the Netherlands**, the Dutch Healthcare Authority (NZa) monitors impact of budget on

delays on access to hospital therapies on an annual basis through hospital surveys (NZa, 2019).

Spain created a dedicated department to coordinate treatment with cell and gene therapies at all stages of treatment, from diagnosis, through rapid confirmation of reimbursement, to ensure delivery of care within 28 days.

In **Germany**, the concept of the tumor conference was established to facilitate access to the center of expertise at the Charité campus of the University Hospital of Berlin. The interdisciplinary online tumor board meetings bring together cancer specialists and practitioners. Following a systematic approach, patient data, relevant external clinical evidence and therapy preference are presented to the participants. An individual therapy recommendation for each patient is reached by consensus discussion (Schroeder, et al., 2011).

5.6 Strengthen collaboration between all stakeholders

As important as it is obvious: stakeholders must collaborate. In each of these priority areas, a concerted effort is needed.

Early collaboration is a crucial instrument to address today's challenges. Current early dialogues and scientific advice should evolve into early collaboration to enable a joint quest for solutions to potential access challenges.

In addition, controversial topics that further constrain stakeholder relations need to be addressed proactively. These comprise questions such as: What do we consider 'true' innovation or value? What are relevant endpoints to measure 'true' innovation? What is a 'fair' price? Where could we increase transparency, and thereby trust, in our current operating system?

Delaying factor(s) addressed

- (#1-10) All delaying factors require stakeholder collaboration
- (#7) Misalignment on value and price: this delaying factor in particular needs to be addressed by stronger collaboration and alignment

Best practices

In **England**, "safe harbour" discussions are used for early engagements between NICE (Early Scientific Advice and Office of Market Access), NHS England and pharmaceutical companies (NICE, 2020).

The **World Health Organization** (WHO) convenes a series of Fair Pricing Forums to enable stakeholders to discuss options for a fairer pricing system for pharmaceuticals (WHO, 2020).

Strengthen collaboration between all stakeholders - recommended next steps

Stakeholders	Next steps
Multi-stakeholder collaborations	Define requirements and platforms for high quality early collaborations focused on problem-solving. Define the aspects (what), objectives (why), pros and cons (how) of transparency. Align on what constitutes 'real' innovation or value and a 'fair' price.

6. Working together to improve access to innovative oncology therapies

To reduce the immense inequalities in patient access between European countries we need to find a common understanding and a common perspective. This is needed because all stakeholders are part of the current system in which we operate and none of the stakeholders involved can solve today's challenges single-handedly.

As described in Chapter 5, all stakeholders have a role to play in realizing the objectives of the six solution areas. They cannot do this in isolation, as actions from one stakeholder are needed for actions by other stakeholders to be successful. In each of the six priority areas, a concerted effort is needed to design and further strengthen effective solutions.

The efforts are summarized per stakeholder and per solution area in Table 4. This overview serves as a starting point. It is a call for further dialogue, analysis and joint problem-solving by all relevant stakeholders in order to further explore the six priority areas.
We need a collaborative approach now. Because for patients, every day counts.

Table 4 None of the priority areas can be realized by one stakeholder in isolation

	1. Align dossier submission timelines	2. Shorten reimbursement timelines	3. Align evidence requirements	4. Be adaptive to rapidly evolving innovation	5. Improve healthcare infrastructures	6. Strengthen collaboration between all stakeholders
Policy makers	Together with all relevant stakeholders, evaluate the advantages and disadvantages of current ERP strategies and explore improvements or alternatives.	Evaluate the access pathway from a process-optimisation perspective and identify opportunities to shorten timelines. Build HTA capabilities. Involve informed patients to maintain a sense of urgency at every step of the access pathway.	Politically support joint clinical assessments and approval of a fit-for-purpose EC Regulation on HTAs.	Collaborate to define clear joint reimbursement criteria. Make real-world data (RWD) collection integral to the introduction of new innovations.	Appoint an authority for improving screening and diagnosis.	Work with national authorities to evaluate the advantages and disadvantages of current ERP strategies and explore improvements or alternatives. Harmonise and align the collection of RWD. Define requirements and platforms for high quality early collaborations focused on problem-solving. Define the aspects (what), objectives (why), pros and cons (how) of transparency. Align on what constitutes 'real' innovation or value and a 'fair' price. Involve patient organisations and representatives in all parts of decision-making and create clarity on what is required when from patient representatives in terms of knowledge, role, and commitment.
Regulators and HTA bodies			Internationally exchange and create consensus on requirements and assessment methodologies.	Develop a comprehensive system of horizon scanning, early collaboration, managed access schemes, and RWD generation to be ready for novel therapies.		
Payers					Identify centres of excellence and ensure optimal accessibility of expertise.	
Pharmaceutical companies	Build HTA capabilities to allow for more dossier submissions in parallel across European countries once ERP as a bottleneck is addressed.	Have the dossier ready in time and submit as soon as national timelines permit.	Submit pharmacotherapeutic dossiers through EUnetHTA or a future European HTA coordination mechanism. Design trials which fit the joint requirements.	Prepare strong evidence-generation plans for effective early collaborations. Prepare well-substantiated pricing and financing proposals that address payer concerns.	Ensure robust clinical data to enable decisions on inclusion in the guidelines. Take payer concerns into account when developing price proposals.	
Healthcare professionals/ Scientific associations					Define a streamlined process to allow for regular updates of clinical guidelines and ensure the resources required.	
Patient organisations		Educate and support authorities regarding the engagement of informed patients at every step of the access pathway.		Generate and publish real-world, patient-generated data.	Monitor the impact of budget scarcity/depletion on patient access.	
Academics and experts	Identify alternative solutions for ERP.			Support the development of clear reimbursement criteria.		

ACCESS FOR PATIENTS

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Disclaimer: this publication is the result of a multi-stakeholder collaboration but does not necessarily reflect the views of individual organisations or persons involved through sounding board meetings.

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Glossary

Access

Access refers to patients having access to the right therapies at the right time. For the purpose of this report, access is measured by:

- Market Access: the proportion of oncology therapies that received a European marketing authorisation and are reimbursed in a country.
- Time to Market Access: the number of days elapsing from the date of EU marketing authorisation to the day of completion of administrative processes related to a positive reimbursement decision.
- Patient Access: the actual use in the first twelve months after the first patient is treated under a reimbursement scheme.

Reimbursement refers to a formal reimbursement scheme, thereby excluding early access schemes as these schemes often reimburse on a case-by-case or restricted basis without completion of the formal HTA procedure.

Agnostic therapy

See 'Tumor-agnostic therapy'.

Biomarker

A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process, or of a condition or disease. A biomarker may be used to see how well the body or a patient responds to a treatment for a disease or condition. An example is the prostate-specific antigen (PSA), which is measured to screen for prostate cancer, as high PSA levels could be a sign of prostate cancer. The key issue at hand is determining the relationship between any given measurable biomarker and relevant clinical endpoints.

Budget impact

The impacts of the new therapy on the health budget.

CAR-T

CAR T-cell therapy is a cancer treatment that uses a patient's own immune system cells (T cells), after these cells have been modified to better recognise and kill the patient's cancer. The T cells are engineered in the laboratory and then expanded to large numbers and infused back into the patient. CAR stands for chimeric antigen receptor, which represents the genetically engineered portion of the T cell. Once in the body, the CAR T cells can further grow to large numbers, persist for long periods of time, and provide ongoing tumour control and possible protection against recurrence.

Clinical endpoint

An endpoint is the primary outcome that is being measured by a clinical trial. Overall survival (OS) is often considered the most common and most meaningful clinical endpoint in cancer.

Clinical efficacy

Clinical efficacy describes how a medication performs in an idealized or controlled setting: a clinical trial.

Clinical effectiveness

Clinical effectiveness describes how medication performs in a real-world setting where patient populations and other variables cannot be controlled.

Clinical guideline

Recommendations on how to diagnose and treat a medical condition, often written by and for doctors but also used by other health care professionals. Guidelines summarize the current medical knowledge, weigh the benefits and harms of diagnostic procedures and treatments, and give specific recommendations based on this information, supported by scientific evidence. Because of the evolving medical knowledge and scientific evidence, clinical practice guidelines must be updated regularly. Guidelines aren't legally binding, but deviations from guidelines must be justified.

Clinical trial

Clinical trials are studies to test new treatments and evaluate their effects on human health outcomes. They need to be approved before they can start, and people (called subjects) volunteer to take part. There are 4 phases of biomedical clinical trials:

- Phase I studies usually test new drugs for the first time in a small group of people to evaluate a safe dosage range and identify side effects.
- Phase II studies test treatments that have been found to be safe in phase I but now need a larger group of human subjects to monitor for any adverse effects.
- Phase III studies are conducted on larger populations and in different regions and countries, often the last step right before a new treatment is approved.
- Phase IV studies take place when, after approval, there is a need for further testing in a wide population over a longer timeframe.

The Randomised Controlled Trial (RCT) is considered the most powerful form of a clinical trial (see: 'Randomised Controlled Trial').

Clock stop

A period of time during which the evaluation of a medicine is officially stopped, while the manufacturer prepares responses to questions from the agency. The counting of the number of days resumes when the applicant has sent its responses.

Companion diagnostics

A companion diagnostic is a diagnostic test, used in combination with a therapeutic drug, to prospectively help predict likely response or severe toxicity or to monitor patients' responses for the purpose of adjusting treatment. Companion diagnostics assist in making optimal treatment decisions.

Cost-based pricing

An approach for determining prices for pharmaceutical products, based on costs incurred for research and development. In

doing so, costs incurred for research and development are rewarded rather than the added value for patients (see: 'value-based pricing'). The starting point for price negotiations should be an agreement among all parties about how much it costs to develop a new medicine. Another challenge is that the approach may lead to the wrong incentives: the higher the R&D costs (e.g. based on medicines that failed to make it to patients), the higher the price that theoretically could be justified.

Cost-effectiveness

Cost-Effectiveness Analysis (CEA) quantifies the gains, or regressions, in population health as a result of an innovative therapy against the cost of this therapy. The gains are typically measured in quality-adjusted life years (QALYs). Subsequently, the net costs of the therapy per QALY are quantified. It provides a method for prioritizing the allocation of resources to therapies, by identifying therapies that have the potential to yield the greatest improvement in health for the least resources.

Cross-over

In oncology randomised controlled trials (RCTs) offering patients the opportunity to cross over to treatment from the other arm at disease progression is a routine practice to address ethical issues. In this situation, it is common to justify that the intervention has a PFS benefit but not an overall survival (OS) benefit due to the crossover. However, some argue that "real" innovations could impact in OS despite crossover, and that minor gain in PFS should not be considered relevant.

Dossier

A reimbursement or value dossier presents a summary of the clinical, economic, and societal value and supporting evidence (studies) for a new therapy, as well as background information on that disease (i.e., burden of illness, epidemiology, etc.) in line with the agency requirements.

Drug Rediscovery Protocol (DRUP)

In 2016, the Drug Rediscovery Protocol was launched in the Netherlands. This is an innovative pan-cancer clinical trial that seeks to expand the use of EMA and/or FDA-approved targeted therapies beyond their approved indications. In the DRUP, patients with metastasized cancer, with a specific tumour and mutational profile, and without any further treatment options, are given a medicine that was registered for another cancer type. The aim is to identify and provide access to potentially effective therapies. Patients are enrolled in parallel groups (cohorts) defined by study drug, tumour type and tumour profile. A cohort starts with eight patients and is doubled in size when efficacy targets are met. If the larger cohort also meets efficacy targets, the study continues. Manufacturers finance the first studies in eight and sixteen patients. When the study continues, the therapy is reimbursed for patients benefiting from it.

Early Access Schemes

In many European countries, patients can gain access to oncology medicines through early access schemes before the medicine/indication is covered or sometimes before it is approved. Such schemes may be limited to medicines treating severe diseases, for which no effective treatments are available. Oncology products often meet these criteria, making them eligible for early access mechanisms. The programs are called "early access scheme", "compassionate use program", "temporary authorisations for use", or "named patient programs". The various programs can be differentiated based on their breadth (available to a large cohort of patients vs. for individual patients only) and source of funding (donation from pharmaceutical companies vs. financed by the authorities). These programs are no substitute for general coverage, since prior authorisation is required for individual patients thereby limiting the breadth of access and making access significantly more complex for prescribers and patients (e.g. in named patient programs) and/or because the financing is based on donation from pharmaceutical companies.

Early collaboration

An updated form of today's early dialogue, symbolizing a move from scientific advice on clinical development plans towards broader discussions between stakeholders prior to EU marketing authorisation, with the aim of aligning on challenges and jointly finding solutions (e.g. managed access scheme, novel payment models). Ideally, early dialogues are used to (i) arrive at an equal level of understanding of the therapy, (ii) jointly identify potential access barriers and solutions, and (iii) identify implications for the assessment and set-up of the clinical trial and phase IV evidence generation plans.

Early dialogue (or Scientific Advice)

Early dialogues (or scientific advice procedures) are a fee-based service offered by regulators and HTA agencies to manufacturers. During early dialogues, a non-binding scientific advice is provided before the start of a pivotal clinical trial, in order to improve the quality and appropriateness of the data produced by the manufacturer in view of future HTA assessment.

European marketing authorisation

A European marketing authorisation is granted when the European Medicines Agency (EMA) has positively evaluated i) Quality: Is the quality of the manufacturing process up to standards? ii) Safety: Is the therapy safe? iii) Clinical efficacy: Is the therapy effective? This regional authorisation takes away the requirement to seek marketing authorisation for new medicines from each Member State separately.

Event-free survival (EFS)

The length of time, after finalising an oncology therapy, that the patient remains free of certain complications or events that the treatment was intended to prevent or delay. These events may include the return of the cancer or the onset of certain symptoms, such as bone pain from cancer that has spread to the bone. In a clinical trial, EFS is one clinical endpoint that can be used to see how well a new treatment works.

Evidence gap

Gaps between the evidence presented in a reimbursement dossier and the evidence requirements from an HTA agency. Evidence gaps may lead to a negative reimbursement decision, a delayed decision due to additional data collection, or a positive decision on the condition that a Phase IV study takes place for further evidence generation and to close the evidence gap.

Evidence requirements

Evidence requested by HTA agencies in order to inform a (positive) reimbursement decision.

External Reference Pricing

The use of medicine price(s) in one or more other countries to serve as a benchmark or reference price for setting or negotiating the price of the product in a given country. List prices are used rather than the net transaction prices. The number of countries considered in the basket varies across countries (ranging from 3 to 30 countries), as does the frequency of price revisions. External Reference Pricing is used in Europe, but European countries are also referenced by non-European countries.

Also referred to as International Reference Pricing.

Health Technology Assessment

A multidisciplinary process that assesses and appraises information about the medical, social, economic and ethical issues related to the use of a health technology in a systematic, transparent, unbiased, robust manner. It informs the final reimbursement decision.

Horizon scanning

The process of identifying new medicines or new uses of existing medicines that are expected to receive marketing authorisation in the near future and gathering preliminary information about their clinical properties, costs, expected benefits, and broader health system impact. Horizon scanning is often used to systematically assess the potential impact of new technologies, to identify which technologies will be subject to a national HTA process and to strategically plan for HTA and health system resources and capabilities.

Incremental Cost-Effectiveness Ratio (ICER)

The incremental cost-effectiveness ratio (ICER) is a statistic used in cost-effectiveness analysis to summarise the cost-effectiveness of a health care intervention. It is defined by the difference in cost between two possible interventions, divided by the difference in their effect. Costs are usually described in monetary units, while effects can be measured in terms of health status or another outcome of interest. A common application of the ICER is in cost-utility analysis, in which case the ICER is synonymous with the cost per quality-adjusted life year (QALY) gained.

Indication

Specific setting in which a medicine is used. One medicine can receive multiple EMA authorisations for different tumour locations, types or stages (indications).

Joint Advice (or Parallel Advice)

Scientific advice from a range of agencies at the same time.

Life-Years Gained (LYG)

Life Years gained (LYG) is a mortality measure where remaining life expectancy is considered. This method accrues more weight to a younger patient. It expresses the additional number of years of life that a person lives as a result of receiving a treatment. It is used in economic evaluation to assess the value of medical interventions.

List price

The formal price a drug manufacturer initially sets and that is publicly available. The list price of a drug greatly differs from the net price, which incorporates discounts and rebates. These discounts and rebates can be mandated by governments during reimbursement discussions, negotiated with insurers and hospitals, and/or voluntarily offered to patients. The discounts and rebates are confidential, to avoid any negative impact on prices in other countries based on external reference pricing, which is most often based on publicly available list prices.

Managed access schemes

Alternative, prospectively planned, iterative approaches to medicines development and data generation for a specific set of medicines to which the criteria for a managed access scheme apply. The aim is to achieve an optimal balance between timely access for patients who are likely to benefit most from the medicine and the need to provide adequate evolving information on the benefits and risks of the medicine itself. It often refers to the generation of evidence after marketing authorisation for therapies for which clinical uncertainties exist at the

time of reimbursement discussions, e.g. with the use of patient registries or performance-based agreements. So far, most of the agreements are financial in nature and aim to mitigate risks on budget impact (e.g. volume-price agreements) (OECD, 2020).

Medical need (unmet medical need)

Chronically or seriously debilitating diseases or diseases considered to be life threatening and that cannot be treated satisfactorily by an existing (approved and reimbursed) pharmaceutical product are considered and area of high (unmet) medical need.

Morbidity

Morbidity refers to the degree of adverse health. It is not directly related to mortality but may over time increase the risk of death.

Mortality

Mortality refers to the risk of death.

Net price

The price that is received by a drug manufacturer, after deduction of discounts and rebates. These confidential discounts and rebates can be mandated by governments during reimbursement discussions, negotiated with insurers and hospitals, and/or voluntarily offered to patients. The discounts and rebates are confidential, to avoid any negative impact on prices in other countries based on external reference pricing.

Network Meta-Analysis (NMA)

A network meta-analysis (NMA) combines numerical data from multiple separate studies, to compare three or more treatments. It uses direct comparisons within randomized controlled trials (RCTs) and indirect comparisons across trials based on a common comparator.

Orphan designation

A status assigned by the EMA to a medicine intended for use for a rare condition, typically based on prevalence criteria as per the EU Orphan Regulation No 141/2000. This regulation was introduced to incentivize research for rare diseases, through e.g. protocol assistance, fee waivers and 10 years market exclusivity.

Overall survival (OS)

The length of time from either the date of diagnosis or the start of treatment for a disease, such as cancer, that patients diagnosed are still alive. In a clinical trial, measuring the overall survival (OS) is one way to see how well a new treatment works. It is often considered the most common and most meaningful clinical endpoint in cancer.

Parallel Advice

See “Joint Advice”.

Post-hoc subgroup analysis

The analysis of subgroups in clinical trials is essential to assess differences in treatment effects for distinct patient groups. It is done

i) to demonstrate consistent results over e.g. male and female, young and elderly patients;
ii) to identify patient subsets with a particular treatment effect, either positive or negative; or
iii) to identify patient subsets with a significant treatment effect when this treatment effect is not present in the overall patient population.

Especially with targeted therapies, manufacturers do not always know upfront which subgroup responds best to the treatment. However, these subgroup analyses specified after trial completion are met with concerns, as the number of patients may be too small to arrive at generalisable conclusions (‘limited statistical power’), or because it may be chosen to best fit a

hypothesis whilst in fact being a result of statistical play of chance.

Progression Free Survival (PFS)

The length of time during and after the treatment of a disease, such as cancer, that a patient lives with the disease but it does not get worse. In a clinical trial, measuring Progression Free Survival (PFS) is one way to see how well a new treatment works.

Quality-Adjusted Life Year (QALY)

The quality-adjusted life year (QALY) is a generic measure of disease burden, including both the quality and the quantity of life lived. It is used in economic evaluation to assess the value of medical interventions. One QALY equates to one year in perfect health. QALY scores range from 1 (perfect health) to 0 (dead).

Randomised Controlled Trial (RCT)

A study in which people are allocated at random (by chance alone) to receive one of several clinical interventions. One of these interventions is the standard of comparison or control. The control may be the standard of care, a placebo ("sugar pill"), or no intervention at all. RCTs seek to measure and compare the outcomes after the participants receive the interventions.

Relative clinical effectiveness

The extent to which an intervention does more good than harm compared with one or more alternative interventions under the usual circumstances of healthcare practice.

Real-World Data (RWD)

Data obtained outside the context of randomized controlled trials (RCTs) and generated during routine clinical practice.

Real-World Evidence (RWE)

Evidence obtained from real world data (RWD).

Reimbursement

European countries need to make evidence-based decisions on public healthcare expenditures. To inform reimbursement decisions for innovative oncology therapies, typical questions that need to be answered by national HTA bodies are:

i) Medical need: Does this therapy address a health need?
ii) Relative clinical effectiveness: Is it more effective than current therapies?
iii) Cost-effectiveness: Is the price a good reflection of the added value?
iv) Budget impact: Could we afford the overall costs of this therapy?

This is done separately by each country. How countries make these decisions varies, leading to significant disparities in patient access throughout Europe.

Reimbursement criteria

Health Technology Assessment (HTA) should be an unbiased and transparent exercise. Therefore, predefined decision-making criteria are formulated to allow for rational, consistent and transparent reimbursement decisions based on e.g. (unmet) medical need, relative clinical effectiveness, cost-effectiveness, budget impact, societal value and ethical considerations.

Scientific Advice

See: "Early Dialogue".

Standard of care

A treatment process that a clinician should follow for a certain type of patient, illness, or clinical circumstance according to the latest standards. It is the level at which the average, prudent provider in a given community would practice. Or how similarly qualified practitioners would have managed the patient's care under the same or similar circumstances.

Statistical significance

Statistical significance is the likelihood that a relationship between two or more variables (e.g. the effect of a therapy) is not likely to occur randomly or by chance but is instead likely to be attributable to a specific cause.

Surrogate endpoint

A surrogate endpoint is a substitute for a clinical endpoint used in trials where the use of a clinical endpoint might not be possible or practical. Surrogate endpoints do not represent direct clinical endpoints such as overall survival (OS), but instead predict them. For example, tumor shrinkage could be used as a surrogate endpoint for OS. Some surrogates are said to be "established" or "validated," meaning they have been proven to predict clinical benefit. Other surrogates have not been validated but are "reasonably likely" to predict clinical benefit.

Time to Patient Access

Time to Patient Access refers to the time needed for patients to have access to the right therapies. For the purpose of this report, it is measured by:

- Time to Market Access: the number of days elapsing from the date of EU marketing authorisation to the day of completion of administrative processes related to a positive reimbursement decision.
- Patient Access: the actual use in the first twelve months after the first patient is treated under a reimbursement scheme. Reimbursement refers to a formal reimbursement scheme, thereby excluding early access schemes as these schemes often provide reimbursement on a case-by-case or restricted basis without completion of the formal HTA procedure.

Tumor-agnostic therapy

A cancer treatment based on the cancer's genetic and molecular features without regard to the cancer type or where the cancer started in the body. Tumor-agnostic therapy uses the same drug to treat all cancer types that have the genetic mutation (change) or biomarker, regardless of the tissue or location in which the tumor is located.

Transparency Directive

The EU 'Transparency Directive' (Directive 89/105/EEC) aims to ensure the transparency of measures regulating the pricing and reimbursement of medicinal products. It describes the obligation of Member States to adhere to a strict national timeline of max. 180 days between the moment a dossier is submitted and the final decision on pricing and reimbursement. The 180 days exclude time that passes between EU marketing authorisation and dossier submission, as well as time needed by companies to provide additional information ('clock stops').

Value-based pricing

An approach for determining reasonable prices for pharmaceutical products based on the general economic concept that prices of new goods indicate the difference between the value of currently available goods and the value that the new goods provide. In doing so, value is rewarded, rather than e.g. costs incurred for research and development (see: 'cost-based pricing').

Abbreviations

AIFA	Italian Medicines Agency (Italy)
AML	Acute Myeloid Leukaemia
AOTMiT	Agency for Health Technology Assessment and Tariffs (Poland)
ASM	Advanced Systemic Mastocytosis
ASMR	Actual Benefit (L'Amélioration de Service Médical Rendu)
ATU	Temporary Authorisations for Use (Autorisation Temporaire d'Utilisation)
CBG	Medicines Evaluation Board (Netherlands)
CDF	Cancer Drugs Fund
CEA	Cost-Effectiveness Analysis
CHMP	Committee for Medicinal Products for Human Use
CTS	Technical Scientific Committee (Italy)
CUP	Compassionate Use Program
DRUP	Drug Rediscovery Protocol (Netherlands)
EAS	Early Access Scheme
EC	European Commission
EFPIA	European Federation of Pharmaceutical Industries and Associations
EFS	Event-Free Survival
EMA	European Medicines Agency
EOP	EFPIA Oncology Platform
EQ-5D	EuroQol Five Dimensions Health Questionnaire
ERP	External Reference Pricing
EU	European Union
EUnetHTA	European Network for Health Technology Assessment
EUPATI	European Patients' Academy
FDA	Food and Drug Administration (United States of America)
G-BA	Federal Joint Committee (Germany)
GDP	Gross Domestic Product
HTA	Health Technology Assessment
ICER	Incremental Cost-Effectiveness Ratio
ICHOM	International Consortium for Health Outcome Measurement
INAMI/RIZIV	National Institute for Health and Disability Insurance (Belgium)
JCA	Joint Clinical Assessment
LMG	Life-Months Gained
LYG	Life-Years Gained
NCCN	National Comprehensive Cancer Network (United States of America)
NHS	National Health Service (United Kingdom)
NICE	National Institute for Health and Care Excellence (England)
NMA	Network meta-analysis
NPP	Named Patient Program
NT	New Therapies (Sweden)
NZa	Dutch Healthcare Authority (Netherlands)
OECD	Organization for Economic Co-operation and Development
OS	Overall Survival
pCR	Pathological Complete Response
PFS	Progression Free Survival
PRIME	PRIority MEdicines scheme under EMA
PSA	Prostate-Specific Antigen
QALM	Quality-Adjusted Life Months
QALY	Quality-Adjusted Life Years
QoL	Quality of life
RCT	Randomised Controlled Trial
RWD	Real-world data
RWE	Real-world evidence
SEED	Shaping European Early Dialogue
TLV	Dental and Pharmaceutical benefits board (Sweden)
ZIN	National Health Care Institute (Netherlands)

Country codes

AT	Austria
BE	Belgium
BG	Bulgaria
CH	Switzerland
CY	Cyprus
CZ	Czech Republic
DE	Germany
DK	Denmark
EE	Estonia
ES	Spain
FI	Finland
FR	France
GE	Georgia
GR	Greece
HR	Croatia
HU	Hungary
IE	Ireland
IS	Iceland
IT	Italy
LT	Lithuania
LU	Luxembourg
LV	Latvia
MT	Malta
NL	Netherlands
NO	Norway
PL	Poland
PT	Portugal
RO	Romania
SE	Sweden
SI	Slovenia
SK	Slovakia
UK	United Kingdom
UK-ENG	England
UK-SCT	Scotland

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Annexes

Four analyses were carried out to inform the findings presented in this report. The methodologies are described in the following annexes:

A. Country case studies on delaying factors and potential solutions
Authors: Silvia Rohr (Vintura), Christel Jansen (Vintura)

B. Patient Access Indicator
Authors: Christel Jansen (Vintura), Bas Amesz (Vintura)

C. Mapping of differences in evidence requirements in various European jurisdictions
Authors: Sharon Wolters (ASC Academics), Christel Jansen (Vintura), Prof. Maarten Postma (University of Groningen)

D. Impact analysis of improved time to market access
Authors: Sharon Wolters (ASC Academics), Evgeni Dvortsin (ASC Academics), Christel Jansen (Vintura), Bas Amesz (Vintura), Prof. Maarten Postma (University of Groningen)

THE unprecedented speed of innovation in oncology provides an important opportunity for further improvement of outcomes for cancer patients. Yet, no value is derived from innovation if patients for whom a new therapy is intended cannot have access to it. In fact, tremendous differences exist in patient access to innovative oncology treatments with in Europe.

This report brings stakeholders across Europe together around opportunities to improve time to patient access for innovative, value-adding oncology therapies. It focusses on reducing European inequalities in terms of delays in ensuring reimbursement and delays in ensuring actual access once reimbursement is in place.

The report is the result of a collaborative approach by health technology assessment (HTA) bodies, healthcare professional associations, patient organisations, policy makers, former politicians, payers and pharmaceutical companies. Its purpose is to provide a comprehensive and unbiased overview of challenges and solutions, thereby moving away from polarised debates which often occur nowadays.

It describes the ten factors delaying time to patient access and six priority areas to address these delays. In each of these priority areas, a concerted effort is needed. It is not a matter of individual stakeholders taking responsibility within their respective areas of work. It requires stakeholders to break through comfort zones and to actively look for common ground with other stakeholders.

To reduce the important inequalities in patient access between European countries we need to find this common ground and a common perspective. Because all stakeholders are part of the current system and none of the stakeholders involved can solve today's challenges single-handedly. We need a collaborative approach now. Because for patients, every day counts.

The publication is endorsed by the following organisations:

Association of Medical Oncologists (AIOM), Italy
Association of Oncology Nurses (AEOP), Portugal
Central and Eastern European Society of Technology Assessment in Health Care (CEESTAHC)
Digestive Cancers Europe (DICE)
European Association of Nuclear Medicine (EANM)
European Cancer Patient Coalition (ECPC)
European Federation of Pharmaceutical Industries and Associations (EFPIA)
European Patients' Academy (EUPATI), Portugal
European Union of Private Hospitals (EUHP)
EVITA - Hereditary Cancer, Portugal
Hodgkin and Non-Hodgkin VZW, Belgium
Lymphoma Coalition Europe (LCE)
Youth Cancer Europe (YCE)

IMPROVING TIME TO PATIENT ACCESS TO INNOVATIVE ONCOLOGY THERAPIES IN EUROPE

EVERY DAY COUNTS

ANNEXES

These annexes describe the methodologies used for the four analyses that informed the report:

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The annexes do not include the results of the analyses, as these are presented in the main report.

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Table of contents

Annex A: Country case studies on delaying factors and solutions

Authors:
Silvia Rohr (Vintura),
Christel Jansen (Vintura)

Little is known about the reasons behind variances and delays in time to patient access. Therefore, case studies were conducted in six European countries which together represent the diverse access contexts in Europe. Countries selected were England, Italy, the Netherlands, Poland, Portugal and Sweden. Document reviews and interviews with regulators, payers, health technology assessment (HTA) bodies, healthcare professional associations, patient organisations, industry organisations and experts allowed for in-depth understanding of delaying factors, best practices and potential solution areas in these countries. Content analysis of the country findings identified a first set of delaying factors and solution areas, potentially applicable to a broader European context. These were discussed over three multi-stakeholder Sounding board meetings, leading to the identification of the ten delaying factors and six priority areas described in the report.

Research question and methodology

The main questions for the Time to Patient Access initiative to answer were:

- What are the delaying factors for access to oncology therapies?

- What are solution areas and best practices to improve?

Exploratory case studies were conducted in six European countries. Data collection was done based on desk research and interviews with relevant stakeholders: policy makers, regulators, HTA bodies, payers, professional associations, scientific societies, patient organisations and experts.

Country selection criteria

Together, the group of six countries should represent the diverse access contexts in Europe. Europe was defined as the 27 European Union (EU) Member States, plus Iceland, Liechtenstein, Norway, Switzerland and the United Kingdom. A set of selection criteria was defined to guide the country selection. The six countries needed to represent:

1. **A significant part of the European population**
   This was defined as ≥ 30% of the total population of the countries in scope (World Bank, 2020).
2. **All geographical regions**
   To this end, countries were categorised as North, South, East, or West.
3. **Variation in HTA orientation**
   This was defined as having a main focus on clinical effectiveness, cost-effectiveness, or budget Impact (WHO, 2018) (OECD/European Observatory on Health Systems and Policies, 2017) (Huic, 2016).
4. **Variation in access organisation**
   This was defined as having a key role for the national, regional, or local level in making reimbursement decisions (Angelis, Lange, & Kanavos, 2018) (WHO, 2018).
5. **Variation in the number of reimbursed therapies**
   To this end, countries were categorised as having a high, medium, or low number of oncology therapies reimbursed (IQVIA, 2020).
6. **Variation in reimbursement delay**
   To guarantee variation in reimbursement delay, countries were categorised as having a high, medium, or low delays in ensuring reimbursement of oncology therapies (IQVIA, 2020).

Fig 1

A group of six countries was selected that represent the diverse access contexts in Europe

Country	1. Population	2. Region	3. HTA orientation	4. Access organization	5. # of reimbursed therapies	6. Reimbursement delay
Poland	*31% of the total population of the countries in the initial scope*	East	Budget impact	National	Low	Medium
Italy		South	Clinical effectiveness	Regional	Medium	Medium
Portugal		South	Clinical effectiveness	National	Low	High
UK (England)		West	Cost-effectiveness	National	High	Low
Nether-lands		West	Cost-effectiveness	Local	High	Low
Sweden		North	Cost-effectiveness	Regional	Medium	Medium

As a first step, per region only the four largest countries were selected to ensure that the group of countries would represent a significant part of the European population. Subsequently, a group of countries was identified that best represented the diverse access contexts in Europe: England, Italy, the Netherlands, Poland, Portugal and Sweden (see Figure 1).

Data collection and analysis

For each country, data was collected using document review and stakeholder interviews. Targeted stakeholder groups were regulators, payers, HTA bodies, healthcare professional associations, patient organisations, industry organisations and experts.

Data was collected on:

- Access pathway: Organisation of the access process for oncology therapies
- Delaying factors: Factors that delay the national access process for oncology therapies
- Best practices: Current initiatives and best practices to optimise time to patient access in oncology
- Solutions: Suggestions for optimising time to patient access in oncology

The information was captured in six country profiles comprising the four above-mentioned chapters. Based on the information in the country profiles, a compilation of the information across countries was made for two themes: delaying factors and solution areas. The latter category comprised both best practices and solutions. Content analysis was used to identify emerging themes and relations between themes. Subsequently, these themes were used to arrive at a first set of delaying factors and solution areas.

To test their relevance and applicability to a broader European context, the initial findings were discussed during three multi-stakeholder Sounding board meetings.[1] These led to the identification of the ten delaying factors and six priority areas described in the report.

1 All sounding board participants are listed in the List of contributors in the main report.

Table 1 In total, 31 interviews were held with 35 stakeholders from six countries

Country#		Organisation	First name	Last name
England	1	Acute leukaemia Advocates Network (ALAN)	Zack	Pemberton-Whiteley
	2	NHS Eastern Cheshire Clinical Commissioning Group (CCG)	Graham	Duce
	3	Salus Alba HTA Consultancy	Andrew	Walker
	4	Association for Cancer Surgery (BASO)	Zaed	Hamady
	5	ABPI	Paul	Catchpole
Italy	6	Associazione Contro il Melanoma	Antonella	Romanini
	7	Italian Association of Medical Oncologists (AIOM)	Roberto	Bordonaro
	8	University of Rome and University of Ferrara	Fabrizio	Gianfrate
	9	Farmindustria	Antonella	Moroni
The Netherlands	10	Dutch Society of Medical Oncology (NVMO)	Haiko	Bloemendal
	11	Medicines Evaluation Board (CBG)	Kevin	Liebrand
	12	Dutch federation of cancer patient organisations (NFK)	Pauline	Evers
	13	Royal Dutch Pharmacists Association	Laurien	Rook
	14	Agendia	Caroline	V.d. Meijden
	15	Association for Innovative Medicine (VIG)	Wim	De
Poland	16	Alivia - Oncology Foundation	Wojciech	Wiśniewski
	17	Central and Eastern European Society of Technology Assessment in Health Care (CEESTAHC)	Magdalena	Wladysiuk
	18	Meritum L.A. Ltd	Krysztof	Łanda
	19	Institute of Mother and Child and Warsaw University of Technology	Marcin	Czech
	20	INFARMA	Ewa	Kiersztyn
Portugal	21	Assembly of the Republic, Portugal	Ricardo	Baptista
	22	EUPATI	Natacha	Vaz Liti
	23	EVITA - Hereditary Cancer	Tamara	Hussong
	24	Infarmed	Rui Santos	Ivo
	25	Portuguese Association of Hospital Administrators (APAH)	Alexandre	Lourenco
	26	Apifarma	Paula	Costa
Sweden	27	Dental and Pharmaceutical Benefits Agency (TLV)	Niklas	Hedberg
	28	Lung Cancer Association	Yann	Fränckel
	29	New Therapies Council (NT Council)	Gerd	Larfars
	30	Swedish Council for Health Technology Assessment (SBU)	Jan	Liliemark
	31	LIF	Johan	Brun

Annex B: Patient Access Indicator

Authors:
Christel Jansen (Vintura),
Bas Amesz (Vintura)

Whilst we know the rate of Market Access and time to Market Access for innovative oncology therapies quite well based on the annual EFPIA W.A.I.T. Indicator Study (IQVIA, 2020), no analysis was available of European differences in actual use after reimbursement (Patient Access). To address this information gap, a European benchmark analysis was made to compare post-reimbursement use between countries, for a set of innovative oncology therapies.

Research question and methodology
The main question for the benchmark was:

- After reimbursement, what are the differences in use between European countries?

For this benchmark, 'use' was measured by analysing volume sold per month (or patients treated per month, based on volume sold), using routinely collected business information from pharmaceutical companies and data providers. 'Post-reimbursement' was defined as the phase that starts when the first patient is treated under a formal reimbursement scheme[2].

This definition excludes the period after a positive reimbursement decision during which all necessary preparations are made to implement the decision[3]. Formal reimbursement refers to the fact that early access schemes are excluded, as these schemes often reimburse on a case-by-case or restricted basis without completion of the formal HTA process.

Country and therapy selection criteria
Europe was defined as the 27 European Union (EU) Member States, plus the United Kingdom, Norway, Iceland, Serbia and Switzerland. As data was easier accessible for larger countries, for each of Europe's geographical regions (East, North, South, West) the four countries with the largest population were included in the benchmark, making sixteen countries in total. These sixteen countries are: Czech Republic, Denmark, Finland, Germany, Greece, France, Hungary, Italy, the Netherlands, Norway, Poland, Portugal, Romania, Spain, Sweden and the United Kingdom (England).

Oncology therapies were included based on meeting the following four criteria:

1. Received a positive opinion from the European Medicine Agency (EMA) Committee for Medicinal Products for Human Use (CHMP) between 2013-2017 (n=98) (SMS Oncology, 2019) (EMA, 2019)
2. Were new active substances (n=53) (SMS Oncology, 2019) (EMA, 2019)
3. Are currently owned by one of members of the European Federation of Pharmaceutical Industries and Associations (EFPIA) Oncology Platform involved in the Time to Patient Access initiative (n=28)
4. Manufacturer is willing and able to share uptake data (n=13)[4]

The thirteen therapies cover Leukaemia (n=4), Breast cancer (n=3), Lung cancer (n=3), Bladder cancer (n=1), Multiple myeloma (n=1), Melanoma (n=1), Non-melanoma skin cancer (n=1) and Ovarian cancer (n=1):

- alectinib
- atezolizumab
- cobimetinib
- daratumumab
- ibrutinib
- midostaurin
- obinutuzumab
- olaparib
- osimertinib
- pertuzumab
- trastuzumab-emtansine
- venetoclax
- vismodegib

Data collection and analysis
- Per therapy, manufacturers shared the following information for the sixteen countries:
- Reimbursement status and date of positive reimbursement decision
- Date of first patient accessing the therapy under a formal reimbursement scheme
- Volume sold per month (or patients treated per month, based on volume sold)[5]

Subsequently, the data was assessed for:

- **Completeness:** out of the 208 (13*16) country-therapy combinations, 87 had to be excluded because the therapy was not reimbursed, or because the dataset was incomplete.
- **Robustness:** it was decided that for countries to be included, the dataset should include at least 50% of the therapies (n=7) to have a robust enough average level of real-world access. Based on this criterium, 6 countries had to be excluded from the analysis: DK, FI, HU, NO, PT, RO (25 country-therapy combinations in total).
- **Quality:** volume datasets that did not capture all relevant sales channels (e.g. in-hospital and retail) were excluded. Furthermore, one country-therapy combination formed an outlier in terms of volume sold that could not be explained and therefore had to be excluded. In total, six additional country-therapy combinations had to be excluded (all remaining countries still adhered to the 'robustness' criterium).

For the ten remaining countries (90 country-therapy combinations), the cumulative use at twelve months post-reimbursement was calculated for each therapy in the dataset. These figures were standardised by correcting for population size.

During the analysis, the data was also corrected for epidemiological differences. Reliable and comprehensive epidemiological data were available at the level of the main cancer types only (IARC Global Cancer Observatory). However, using this data would not provide an accurate correction for epidemiological differences between countries, since epidemiological differences between countries for the sub-types and specific biomarkers in scope of the analysis may very well differ from the differences at the level of the broader cancer type. Therefore, in the end it was decided not to correct for epidemiological differences, to avoid 'pseudo-accuracy'.

The data was not corrected for the content of the positive reimbursement decision (size of the eligible population, number of reimbursed indications) for two reasons. First, because these decisions are an important driver that need to be captured when demonstrating differences in patient access. Secondly, sales

2 In most countries, a reimbursement scheme is in place after finalization of the HTA and reimbursement process. Germany is an exception, as the therapy is automatically reimbursed after EC Marketing Authorization, pending finalization of the HTA procedure and reimbursement process.

3 This period is covered by the Patients W.A.I.T. indicator (IQVIA, 2020).

4 One therapy has multiple cancer sites as a main indication.

5 The data for the United Kingdom was corrected by excluding Scotland from the data. This was done by deducting an uptake curve for Scotland from the UK uptake curve, as of the moment of a positive reimbursement decision by the Scottish Medicine Consortium. The Scottish uptake curve was assumed to be 8% of the UK uptake curve, in line with the size of the population.

information is most often not available per indication, hampering a comparative analysis of volume per specific indication.

The data per country and per therapy, corrected for population size, was shared with the respective pharmaceutical companies to allow for validation.

Subsequently, per therapy, the cumulative use at twelve months post-reimbursement in the ten countries was expressed as a relative use compared to the country with the highest use of that therapy. And finally, per country, the average relative use across all therapies was calculated to arrive at one single indicator of post-reimbursement use compared to other countries.

The outcome of the analysis is shown in Figure 2.

Two important aspects should be considered when interpreting the findings of the analysis.

First, the benchmark illustrates **differences rather than best practices**. High clinical use for a specific therapy does not equal optimal access. High clinical use can also be a symptom of a suboptimal access situation, e.g. when a more advanced treatment option such as stem cell transplantation (in the case of haematology) is not available or accessible.

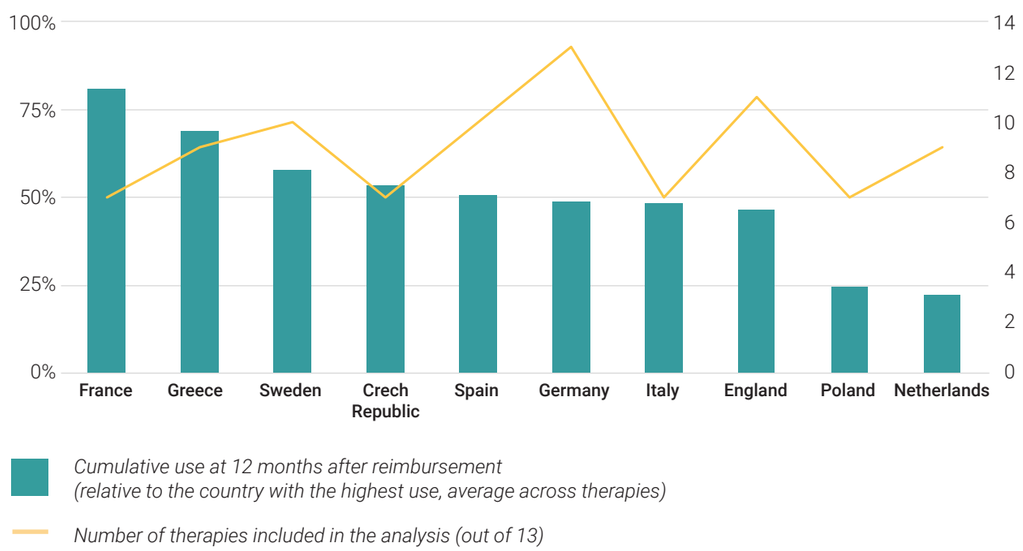
Countries with the highest clinical use per therapy were set as the benchmark country (100%) to enable comparison, not to set a standard or best practice. However, since the benchmark covers multiple therapies in multiple indications, it provides a good indication of health system factors delaying time to patient access.

Second, the outcomes serve as the **start of further research and discussions** on European inequalities regarding post-reimbursement clinical use. They give a quantitative overview of the differences, without explaining the reasons behind these variances.

Fig 2

Patient Access Indicator

What are country differences in cumulative use, 12 months after a positive reimbursement decision?



Annex C: Mapping of differences in evidence requirements in various European jurisdictions

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One cause for delays in patient access concerns the differences in evidence requirements across Europe. Obviously, the evidence required by the EMA to demonstrate clinical efficacy and inform a marketing authorisation decision differs from the evidence required by national HTA bodies to demonstrate clinical effectiveness and inform reimbursement decisions.

Yet more importantly, also among HTA bodies, who all aim to answer similar evaluation questions, evidence requirements vary. When evaluating clinical effectiveness, HTA bodies assess whether the evidence provided is robust enough to proof that the therapy is more effective than existing alternatives (e.g. the current standard of care). They look at the patient population that was studied, the comparator therapy that was used, the clinical endpoints (outcomes) that were measured, the way in which the trial was set-up, and the statistical anlyses that were run.

However, the evidence that is considered robust or acceptable varies greatly across Europe. To illustrate and analysis this, a comparative analysis of evidence requirements was performed for EMA and six European HTA bodies. For the seven agencies, it was assessed whether certain evidence characteristics would be accepted as convincing evidence. Data was collected using desk research and interviews with agency representatives. Findings were summarised, categorised and mapped. This allowed for visualisation and quantification of differences in evidence requirements across a set of agencies in Europe.

Research question and methodology

The main question for this comparative analysis was:

- What are differences in evidence requirements for oncology therapies in various European jurisdictions?

Sub questions were:

- To what extent are evidence requirements aligned between EMA and HTA bodies?
- To what extent are evidence requirements aligned among HTA bodies?

In order to answer these questions, a comparative analysis of evidence requirements was performed for EMA and six European HTA bodies.

Evidence required was defined as the minimum level of evidence that is accepted as convincing evidence. To test the respective evidence requirements, a set of nineteen evidence characteristics was developed. These nineteen characteristics were developed using existing frameworks from Shaping European Early Dialogue, SEED (HTA International, 2015) and Tafuri et al. (Tafuri, et al., 2016). An overview of the nineteen characteristics is provided in Table 2. Details per element can be found in Table 5. For all agencies, it was assessed whether these characteristics would be accepted and at which conditions.

Country and therapy selection criteria

The six case study countries selected for the Time to Patient Access initiative were included in the analysis, together with EMA.

Data collection and analysis
Data collection took place through desk research and interviews with agency representatives. Per agency, data was collected on:

- Acceptance: are the different evidence characteristics accepted and at which conditions?
- Challenges, trends and recommendations in relation to evidence requirements in oncology.

In total, seven interviews were held with ten representatives from the seven agencies, or subject matter experts. In the case of Poland, it was not possible to include a representative from the Agency for Health Technology Assessment and Tariff System (AOTMiT). Therefore, a well-known Polish HTA expert was interviewed.[6] The respondent from the EMA CHMP participated on a personal title (rather than as a formal representative) and wished to remain anonymous.

An overview of the agency representatives interviewed for the purpose of this analysis can be found in Table 3.

6 Prof. Marcin Czech is head of the Department of Pharmacoeconomics at the Institute of Mother and Child in Warsaw.

Table 2 Acceptance of nineteen evidence characteristics was tested across six European HTA bodies and EMA

Domain	Characteristic
Population	• Target population as authorised by EMA • Use of biomarkers • Extrapolation to other populations
Comparator	• Selected comparator • Class effects • Indirect comparison
Endpoints	• Progression-free survival (PFS) as endpoint • Other surrogate endpoints • Absence of quality of life (QoL) data
Trial design	• Real-world evidence • Network meta-analysis (NMA) • Single-armed trials • Novel trial designs • Cross-over in trials • Evidence from small populations • Short time period
Statistical analysis	• Absence of statistical significance • Post-hoc subgroup analyses • Clinical relevance of the effect size as assessed by EMA

Source: ASC Academics.

Table 3 In total, seven interviews were held with ten stakeholders from seven agencies

Country	#	Organisation	First name	Last name
EU	**1**	One of the EMA Human Medicines Committees (CHMP)	Anonymous	Anonymous
England	**2**	National Institute for Health and Care Excellence (NICE)	Zoe	Garrett
Italy	**3**	AIFA Commissione Tecnico Scientifica (CTS)	Armando	Genazzani
The Netherlands	**4**	National Health Care Institute (ZIN)	Jolanda Pauline	De Boer Pasman
Poland	**5**	Institute of Mother and Child and Warsaw University of Technology	Marcin	Czech
Portugal	**6**	Infarmed	Rui Santos Rita Claudia	Ivo Bastos Furtado
Sweden	**7**	NT Counsil	Jan	Liliemark

Data was analysed using two steps.

Step 1: Categorisation of answers
First, the answers of the respondents were summarised and categorised by SW and CJ. Their categorised answers, together with the answer categories used by others, were presented back to respondents for validation.[7]

Second, the categories were labelled by SW and CJ as 'accepted', 'often accepted', 'case-dependent', 'often not accepted', 'not accepted'. The outcomes can be found in Table 5.

Third, these labels were converted by SW and CJ based on the level of predictability. As a point of departure, by default:

- 'accepted' and 'not accepted' were classified as 'predictable'
- 'often accepted' and 'often not accepted' were classified as 'not fully predictable'
- 'case-dependent' was classified as 'highly unpredictable'.

This was adapted when the default conversion was no longer reflecting the content, e.g. in the case of acceptance of biomarkers or indirect comparisons which are often accepted ("accepted when validated" and "accepted when needed and done in accordance with guidelines" respectively), yet fully predictable.

Step 2: Quantification of the levels of acceptance, predictability and alignment
Subsequently, levels of acceptance were quantified per agency. This was done by calculating the proportion of the 19 evidence characteristics that was classified by the agency as 'Accepted' and 'Often accepted'. Likewise, the level of predictability was

7 In the case of Italy, one last specific validation question was answered by a new respondent (HTA expert from Italy), as it was not possible to receive further inputs from AIFA.

calculated per agency, by calculating the proportion of the 19 evidence characteristics that was classified as 'predictable'.

Finally, per evidence characteristic, the levels of alignment and predictability among agencies were quantified, based on respectively the maximum proportion of countries with the same level of acceptance and the number of countries for which the acceptance was 'predictable'.

The outcomes can be found in Figures 9 and 10 of the main report.

Table 4 The answers of the respondents were categorised and labelled based on the level of acceptability

Legend

Accepted | Often accepted | Case-dependent | Often not accepted | Not accepted

EVIDENCE CHARACTERISTICS (for the clinical- or cost-effectiveness assessment)		AUTHORIZATION	HEALTH TECHNOLOGY ASSESMENT					
		EMA	England	Italy	Netherlands	Poland	Portugal	Sweden
Population	• Target population as authorized by EMA	N/A	Accepted	Often not aligned and restricted to the subgroup that benefits most	Not always aligned; can be restricted to the subgroup that benefits most	Often not aligned and restricted to the subgroup that benefits most	Not always aligned and restricted to the subgroup that benefits most	Not always aligned; can be restricted to the subgroup that benefits most
	• Use of biomarkers	Accepted	Accepted when validated	Accepted when validated	Accepted when validated	Accepted when validated	Accepted when validated	Accepted when validated
	• Extrapolation to other populations	Accepted	Often accepted	Usually not accepted, except for age groups	Case dependent, depending on justification (e.g. children)	Accepted	Usually not accepted, except for rare diseases	Case dependent, depending on justification (e.g. children)
Comparator	• Selected comparator	Best available evidence-based therapeutic option	Standard of care	Drug used in the clinical trial and available in the country	Standard of care	Drug used in the clinical trial and available in the country	Standard of care	Standard of care
	• Class effects	Accepted for safety, rarely considered for effectiveness	Case dependent, creates uncertainty	Not accepted	Case dependent, should be measured separately	Accepted	Not accepted	Case dependent, accepted for 'me-too' drugs
	• Indirect comparisons	Accepted, when needed	Accepted when needed and done in accordance with guidelines	Accepted when needed	Accepted when needed, creates more uncertainty	Accepted when needed and done in accordance with guidelines	Accepted when needed	Accepted when needed and done in accordance with guidelines
Clinical endpoints	• PFS as endpoint	Accepted	Accepted	Often not accepted	Often accepted	Often accepted	Often not accepted	Often Accepted
	• Other surrogate endpoints	Accepted if quantitative correlation	Case dependent	Case dependent	Not accepted	Accepted	Often not accepted	Often accepted
	• Absence of QoL data	QoL is important	QoL is very important	QoL is supportive	QoL is important	QoL is supportive	QoL is important	QoL is important
Trial design and data sources	• Real-world evidence	RWD/RWE is supportive	RWD/RWE is supportive	RWD/RWE is supportive	RWD/RWE is supportive	RWD/RWE is supportive	RWD/RWE is supportive	RWD/RWE is supportive
	• Network Meta-Analysis	NMA are accepted	NMA are accepted, when needed, creates uncertainty	NMA could be accepted	NMAs are accepted, when needed and preferably published	NMA could be accepted	NMA are accepted, when needed	NMA are accepted, when needed
	• Single-armed trials	Accepted, creates uncertainty	Accepted, creates uncertainty	Accepted if evidence is satisfactory	Can be accepted, creates uncertainty	Accepted, but treated as less strong evidence	Usually not accepted	Accepted, creates uncertainty
	• Novel trial designs	Accepted, if evidence is satisfactory	Accepted, creates uncertainty	Accepted if controlled	Case dependent	Accepted if methodology is well-described	Accepted if plausible biological mechanism	Accepted if accepted by EMA
	• Cross-over in trials	Accepted, creates uncertainty	Accepted, creates uncertainty	Case dependent, based on the influence on the interpretability of the results	Can be accepted, creates uncertainty	Accepted, but creates an interpretation challenge	Case dependent, based on the influence on the interpretability of the results	Case dependent
	• Evidence from small populations	Accepted	Accepted, creates uncertainty	Accepted if evidence is satisfactory	Accepted if requirements of GRADE methodology are met	Accepted, creates uncertainty	Accepted if evidence is satisfactory	Accepted if it is the best available evidence
	• Short time period	Accepted, but justification needed	The longer the better, short period creates uncertainty	Case dependent	Hard endpoint should be identified	The longer the better	Clinically relevant in context natural history	The longer the better, short period creates uncertainty, a convincing mean OS should be demonstrated
Statistical analysis	• Absence of statistical significance	Not accepted	Case dependent: No hard cut-off point	Not accepted	Case dependent: Not very decisive (focus on CI)	Not accepted	Not accepted	Not accepted
	• Post-hoc subgroup analyses	Usually not accepted	Usually not accepted	Usually not accepted, unless drug does harm	Not accepted	Usually not accepted, unless request HTA body	Usually not accepted	Usually not accepted, unless request HTA body
	• Clinical relevance of effect size as assessed by EMA	Case dependent	Case dependent: Own assessment, no threshold	Case dependent: Own assessment, no threshold	Own assessment (threshold 3 months OS)	Follows EMA	Case dependent: Own assessment, no threshold	Case dependent: Own assessment, no threshold

Table 5 Detailed description of the nineteen evidence characteristics tested for level of acceptance across six European HTA bodies and EMA

Domain	Characteristic	Definition
Population	Target population as authorised by EMA	For reasons of better effectiveness, evidence or cost-effectiveness in subgroups a target population that is smaller than the population for which marketing authorisation was obtained could receive reimbursement. We asked HTA bodies whether the target population could differ from the population identified by the EMA and for what reasons.
	Use of biomarkers	Oncology is evolving to targeted treatments. For these treatments, biomarkers are necessary to identify the target populations. With the increase in the use of biomarkers come new technical, regulatory and ethical problems (EUPATI, 2020). We asked the respondents whether the use of biomarkers is accepted and at what conditions.
	Extrapolation to other populations	The trial population does not always represent the actual population who will use the drug (e.g. other age groups, other nationalities, subgroups). In these cases, manufacturers will extrapolate the trial population to the actual to be treated population. A limitation of extrapolation is the increase in uncertainty. The respondents were asked if extrapolation to other populations is accepted and at what conditions.
Comparator	Selected comparator	Treatment strategies can differ between countries, resulting in a different replaced treatment/different positioning in the treatment algorithm. The respondents were asked which comparators are acceptable in the assessment (Whatever was used in the trial/best possible care/best standard of care/placebo/other) and if the comparator could differ from the one used in the EMA assessment.
	Class effects	A new drug is claimed to have a similar effect as another, already reimbursed drug (for example me-too drugs). The assessment of these drugs as a class could decrease the assessment time. The respondents were asked if class effects were accepted.
	Indirect comparison	When no, or not the right comparator in the trial is used, a comparison with a drug outside the trial must be made. For this purpose, an indirect comparison can be made. A limitation of indirect comparisons is the difference in trial designs. Respondents were asked if indirect comparisons are accepted and at what conditions.
Endpoints	PFS as endpoint	OS cannot always be measured due to the need for a large patient population, multiple years of accrual and follow-up and higher costs (Gutman, et al., 2013). The PFS could be used as surrogate for overall survival (OS). The respondents were asked if the endpoints accepted by the agency could differ from the ones accepted by EMA and how it differs, for example concerning PFS.
Endpoints (continued)	Other surrogate endpoints	Surrogate endpoints (intermediate endpoints) are not intrinsically beneficial to patients but are designed to be easier and faster to measure than hard endpoints (Kemp & Prasad, 2017). The respondents were asked if surrogate endpoints (besides PFS) (e.g. pathologic complete response and minimal residual disease) are accepted and at what conditions are surrogate endpoints accepted.
	Absence of QoL data	QoL data can be lacking in the assessment, because the completion of a QoL questionnaire takes a lot of energy from a cancer patient, measuring the QoL is very labour intensive for the researchers, and it is costly and challenging to analyse the data (multiple questionnaires can be used and data can be missing). The importance of the use of QoL in the assessment is asked and if so, what method is preferred, such as the EuroQol Five Dimensions Health Questionnaire (EQ-5D).
Trial design	Real world evidence	Evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of real-world data (RWD) (e.g. from electronic health records or product and disease registries) could be used to demonstrate the effect in actual practice. The respondents were asked if real-world evidence (RWE) or RWD is accepted and at what conditions.
	Network meta-analysis	In NMA variable data sources and many variables are included, which makes a stringent meta-analysis in many cases not a feasible approach (EMA, 2001). The respondents were asked whether network meta-analyses are accepted and at what conditions.
	Single-armed trials	With rare cancers and precision medicines, only a small trial population is possible, which makes conduction of a randomised trial impractical. In single-arm trials, researchers could choose to enrol everyone in the trial to the experimental therapy (single-arm trials), potentially also due to ethical arguments. In the absence of comparative data, other endpoints (such as response rates) must be used to be able to demonstrate the clinical impact. We asked the respondents if single-arm trials are accepted, and what best practices apply when only single-arm trials are submitted.

Domain	Characteristic	Definition
	Novel trial designs	Precision medicine comes with a specific issue concerning evidence generation as it is difficult to recruit enough patients with the right tumour subtype in a traditional two-armed trial to secure enough statistical power. Furthermore, the rapid emergence of new technologies hampers the choice of the adequate standard of care (SoC) as the comparator. Novel trial designs (e.g. umbrella trials, basket trials, and adaptive trials) can help reduce the issues created by precision medicine. However, they present some ethical concerns referred to scientific validity and risk-benefit balance (Strzebonska & Waligora, 2019). Respondents were asked if novel trial designs would be accepted and at what conditions.
Trial design (continued)	Cross-over in trials	A trend seen in oncology is switching treatments during the trial (e.g. from placebo to the active drug). Cross-over during the trial may be considered due to ethical reasons but is accompanied by issues such as confounding of the endpoints. We asked the respondent if crossover in a trial is accepted, and what constitutes best practices when crossover is included.
	Evidence from small populations	Precision medicines leads to the use of specific target populations in a clinical trial and therefore to the use of a small trial population. The use of a small trial population is accompanied with several issues, including heterogeneity in the patient population, and difficulty in recruitment. The respondents were asked if EMA-acceptance of evidence obtained from a small target population, also means acceptance by the HTA body or at what conditions it would be accepted.
	Short time period	The use of conditional marketing approval resulted in the use of shorter trial periods/prematurely ending the trial, and immature data. This results in too little information, creating more uncertainty in the efficacy and safety evidence of a product. We asked the respondents what the minimal time periods for measuring endpoints and time to follow-up should be.

Domain	Characteristic	Definition
Statistical analysis	Absence of statistical significance	One could argue that P-values are useful as a pragmatic guide to interpret the results of a clinical trial, not as a strict binary boundary that separates real treatment effects from lack thereof. The interpretation of statistical significance could possibly not do justice to the data (Buyse, et al., 2016). Respondents were asked how decisive statistical significance is in the oncology assessment.
	Post-hoc subgroup analyses	Manufacturers do not always know upfront which subgroup responds best to the treatment. Specific subgroup analyses can be pre-specified. Subgroup analyses specified after trial completion might be used to demonstrate the efficacy of the product in those subgroups. A limitation of post-hoc subgroup analyses concerns the validity and potential absence of pre-specification. We asked the respondents if post-hoc subgroup analyses are accepted and at what conditions.
	Clinical relevance of the effect size as assessed by EMA	The interpretation of the effect size of OS or PFS is sometimes interpreted differently between jurisdictions (Kleijnen, et al., 2016). Respondents were asked if an endpoint (for example OS and PFS) which was considered by EMA to be of large enough magnitude to be labelled as clinically relevant effect size, is also considered large enough/clinically relevant by the HTA body.

Annex D: Impact analysis of improved time to market access

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During reimbursement discussions, minimizing time to patient access can become an abstract objective, whereas for patients, every day counts. To make the potential impact of accelerating reimbursement decisions and hence the time it takes for patients to access new therapies more tangible, an impact analysis was performed. In this analysis, different reimbursement scenarios are applied to real life cases from the past, using two case study therapies. The scenarios have been researched in all six case study countries. The findings show the immense gains from improving time to patient access and serve as a reminder of our common objective and the urgency of addressing delays where we can.

Research question and methodology

The objective of the impact analysis is to assess how much there is to be gained from reducing time to market access. Main research question was:

- If time to market access would have been reduced:
  - how many more patients could have been treated?
  - what would have been the health impact?

An impact analysis was performed in order to answer these questions. In this analysis, different reimbursement scenarios were applied to real life cases from the past, using two case study therapies.

The methodology is visualised in Figure 3. The analysis departs from the date of actual access for the therapy in a country. As of this date, patients began using the therapy under a formal reimbursement scheme. The grey curve represents the number of new patients per month using the therapy (based on an analysis of sales information) as of the actual access date. To this actual situation, a hypothetical scenario of earlier access can be applied. Such a scenario would move the grey uptake curve to the left, as is represented by the orange curve. The area between the orange and the grey curve represents the additional number of patients that could have been treated if time to market access would have been reduced. In order to calculate this area, the same moment in time is to be used as a cut-off point for both scenarios. For the purpose of this analysis, a cut-off point of 5 years was used. This follows from the assumption that all patients have been reached at the start of year five and remains stable for at least another

Fig 3

An analysis was made of potential gains from reducing time to patient access

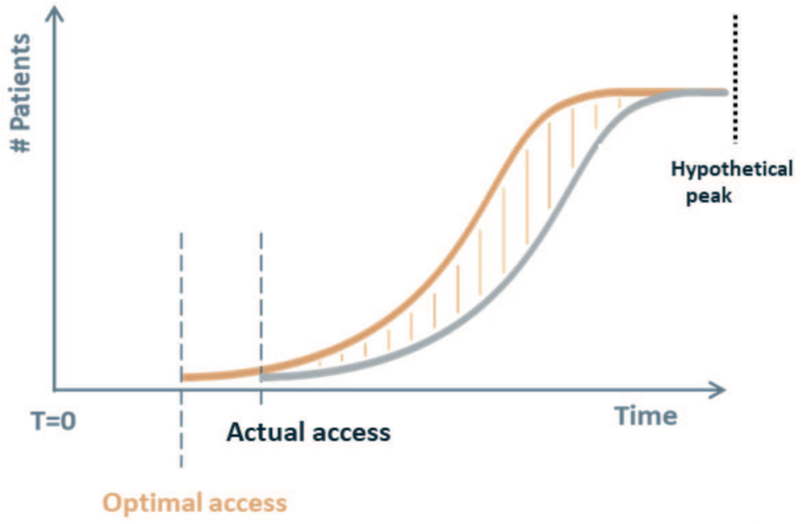

Table 6 Impact analysis of improved time to market access

Concept	Definition	Information source
Time to patient access	The number of days between the date of EU marketing authorisation and the date of access.	EMA website and manufacturer
Access	Access starts when the first patient is treated under a formal reimbursement scheme. It excluded the period after a positive reimbursement decision during which all necessary preparations are made to implement the decision. Formal refers to the fact that early access schemes are excluded, as these schemes often reimburse on a case-by-case or restricted basis without completion of the formal HTA procedure.	Manufacturer
Number of patients treated	Individual new patients per month, using the therapy for the indication under study.	Manufacturer (routinely collected information on actual sales, for the indication under study and translated into new patients per month).
Health impact	Health gains, expressed in terms of OS, event-free survival (EFS), life-years gained (LYG) and/or quality-adjusted life years (QALY) gained, versus the health gains of the comparator. It was determined using information from the country-specific reimbursement dossiers and translated into health gains per month: OS per month, EFS per month, life-months gained (LMG) and quality-adjusted life-months (QALMs).	Country-specific reimbursement dossiers

year (the hypothetical peak in Figure 3). The optimised reimbursement date was defined with the use of three hypothetical scenarios.

- **Scenario A: at the time of the EC marketing authorisation.**

This is the 'highly ambitious' scenario, used to analyse the potential gains of making time to patient access as short as possible. In this scenario, patients would have had access at the time of the European Commission's (EC) marketing authorisation.

- **Scenario B: as fast as the fastest country.**

In this 'best practice' scenario, the potential gains are assessed for a situation in which all countries ensure reimbursement as fast as the fastest country.

- **Scenario C: at 180 days after the EC marketing authorisation.**

This is the 'basic' scenario, representing a situation in which dossiers are submitted directly after EC marketing authorisation and all stakeholders involved adhere to a timeline of max. 180 days between the moment of submission and the final decision on pricing and reimbursement, in conformity with the EC Transparency Directive (European Commission, 1988).

Country and therapy selection criteria

The scenarios have been researched in the six case study countries selected for the Time to Patient Access initiative. For therapies to be included, they needed to adhere to each of the following criteria:

1. EU marketing authorisation issued in 2013-2017 (n=90) (EMA, 2019) (SMS Oncology, 2019)
2. Targeting one of the fifteen most common cancer types in Europe (n=45) (International Agency for Research on Cancer, 2019)
3. Developed by manufacturers who are member of the Time to Patient Access project team (n=21)
4. Manufacturers uptake data available for use (n=3)
5. Reimbursed in at least half of the six case study countries for at least twelve months (n=2)

The following two case study therapies were included:

- Midostaurin, a protein kinase inhibitor used for the treatment of acute myeloid leukaemia (AML) and advanced systemic mastocytosis (ASM). AML is characterised by a rapid growth of abnormal blood cells that build up in the bone marrow and blood and interfere with normal blood cells. As an acute leukaemia, AML progresses rapidly and is typically fatal within weeks or months if left untreated. Around 80% of patients diagnosed with AML pass away within five years (Eurocare, 2020). In September 2017, midostaurin gained a European marketing authorisation with an orphan designation for adult patients with newly diagnosed AML who have a specific (FLT3) mutation (EMA, 2020).
- Pertuzumab, a monoclonal antibody targeting breast cancer characterised by the presence of a specific (HER2) protein. Breast cancer is the most common cancer type in Europe. Almost 90% of all patients diagnosed still live after five years (Nuffield Trust, 2020). In July 2015, pertuzumab gained a European marketing authorisation for treatment of breast cancer when the disease is in the early stage, i.e. is contained in the breast or it has only spread to the lymph nodes in the underarm area. In this stage it is highly treatable, through a combination of surgery and treatment, and often radiation. It was authorised for use in early-stage breast cancer at high risk of coming back, in combination with trastuzumab and chemotherapy, in the neo-adjuvant setting, i.e. before the patient undergoes surgery (EMA, 2019).[8]

Table 7

Input data for the two case study therapies, per country

Country	EC authorisation	Reimbursement date *(source: manufacturer)*	Health gains per patient *(source: reimbursement dossier)*
MIDOSTAURIN			
Italy	18-09-2017 (EMA, 2020)	31-07-2018	49.1 months OS 4.6 months EFS (EUnetHTA, 2017) (AIFA, 2018)
The Netherlands		01-02-2018	49.1 months OS 4.6 months EFS (EUnetHTA, 2017)
Poland		Not reimbursed	-
Portugal		Since 11-09-2019, which is too late for inclusion in the analysis.	- (Infarmed, 2019)
England		04-05-2018	49.1 months OS 5.2 months EFS (NICE, 2018)
Sweden		31-01-2018 (TLV, 2018)	49.1 months OS 5.2 months EFS
PERTUZUMAB			
Italy	28-07-2015 (EMA, 2019)	Not reimbursed	
The Netherlands		01-12-2015	For pertuzumab no assessment document was available/ Therefore the health gains reported by NICE were used (NICE, 2016).
Poland		Since 01-09-2019, which is too late for inclusion in the analysis.	-
Portugal		Not reimbursed	-
England		17-11-2016	0.34 QALY (4.08 quality-adjusted life months, QALMs) 0.47 LYG (5.64 life-months gained, LMGs) (NICE, 2016)
Sweden		03-03-2016	0.30 QALY (3.06 QALMs) 0.71 LYG (8.52 LMGs) (TLV, 2015)

8 In June 2018 pertuzumab was approved in a second indication of early

Data collection and analysis

As described in Table 6, the information on EC marketing authorisation, access and health impact were retrieved from EMA, the manufacturer and the national or EUnetHTA (in the case of midostaurin) assessment reports. Information from assessment reports was retrieved from public sources where possible and complemented by manufacturers when needed. The final input data used can be found in Table 7.

Whereas for pertuzumab for most selected countries relevant data were available, no assessment document was available in the Netherlands. Therefore, the health gains reported by NICE were used. Both documents from NICE and the Dental and Pharmaceutical benefits board (TLV) in Sweden used LYG and QALYs to inform the economic evaluation. Therefore, these health gains were used to inform the impact analysis.[9] For midostaurin, QALYs were not used to inform the clinical assessment by EUnetHTA and were not reported in the assessment documents of NICE and TLV either. Overall OS and EFS were used instead.

Table 7 provides an overview of all input data that was used for the two case study therapies, per country. The table excludes the number of patients treated per month, since this was shared as confidential company data. If this data was available for less than five years, the actual number of new patients treated needed to be extrapolated from the last month of the available uptake till the end of the fifth year. This was the case for midostaurin, for which about one year of uptake data was available. For this, a linear trendline was used, which started at the fourth month to exclude the lowest level of early uptake. Based on exchange with experts from the manufacturer, an assumption was made on the moment at which the maximum number of patients per month would be reached. Based on these discussions, the linear trendline stopped at the assumed peak at the start of year five, after which the number of patients per month was assumed to stabilise.

Results could not be reported if the country had no formal reimbursement of the drug or when less than 1 year of uptake data was available. In the latter case, no extrapolation of uptake data would be possible.

A health economic model was developed in Microsoft® Excel® to calculate for each therapy and country the impact of the three scenarios on the number of patients that could have been treated, and the health impact following from that. This was done using three steps:

1. Calculate the improvement in time to patient access: determine the difference in days between the optimised scenario and the actual scenario.
2. Calculate the number of patients that could have been treated: calculate the area under the curve (see Figure 3)
3. Calculate the health gains: multiply the number of patients with the incremental health gains per month.

breast cancer (adjuvant), but this indication was not considered in the analysis, which focuses on the first, neo-adjuvant indication.

9 The health gains of pertuzumab (QALY and LYG) are calculated using the surrogate endpoint of pathological complete response (pCR). At the time (in 2016) it was assumed to be "reasonably likely" that EFS and OS would improve when pCR improved. Recent studies confirmed this relation between pCR ad EFS (Swain, et al., 2019) (Loibl, et al., 2019)

Abbreviations

AIFA	Italian Medicines Agency (Italy)
AML	Acute Myeloid Leukaemia
AOTMiT	Agency for Health Technology Assessment and Tariff System
ASM	Advanced Systemic Mastocytosis
CHMP	Committee for Medicinal Products for Human Use
CTS	Technical Scientific Committee (Italy)
EC	European Commission
EFPIA	European Federation of Pharmaceutical Industries and Associations
EFS	Event-Free Survival
EMA	European Medicine Agency
EQ-5D	EuroQol Five Dimensions Health Questionnaire
EU	European Union
HTA	Health Technology Assessment
LMG	Life-Months Gained
LYG	Life-Years Gained
NICE	National Institute for Health and Care Excellence (England)
NMA	Network meta-analysis
NT	New Therapies (Sweden)
OS	Overall Survival
pCR	Pathological Complete Response
PFS	Progression Free Survival
QALM	Quality-Adjusted Life Months
QALY	Quality-Adjusted Life Years
QoL	Quality of life
RWD	Real-world data
RWE	Real-world evidence
SEED	Shaping European Early Dialogue
TLV	Dental and Pharmaceutical benefits board (Sweden)
ZIN	Dutch Healthcare Institute (Netherlands)

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