CIRS Centre for Innovation in Regulatory Science

R&D BRIEFING 99

Tracking the Journey:

First HTA Outcomes and Timelines for Oncology Medicines Approved by the EMA (2018–2023)

CONTENT

Introduction

In 2018, the Centre for Innovation in Regulatory Science (CIRS) launched the HTADock project as part of its health technology assessment (HTA) programme. This project has annually explored the synchronisation between the regulatory and HTA landscapes, aiming to understand the process and outcome of HTA while additionally providing context behind the timeline metrics. It has also sought to facilitate the enhancement of performance within HTA agencies.

This R&D briefing continues these efforts and focuses on the synchronisation between the European Medicines Agency (EMA) and European HTA agencies. This briefing analyses publicly available data on oncology new active substances (NASs) approved between 2018 and 2023 by the EMA and their corresponding European appraisals. The agencies involved in this study include: (1) the French Haute Autorité de Santé (HAS), (2) the German Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG), (3) the Irish National Centre for Pharmacoeconimics (NCPE), (4) the Zorginstituut Nederland (ZIN) in Netherlands, (5) the Polish Agencja Oceny Technologii Medycznych i Taryfikacji (AOTMiT), (6) the Portuguese Autoridade Nacional do Medicamento e Produtos de Saude (INFARMED) and (7) the Swedish Tandvårds & läkemedelsförmånsverket (TLV).

In the following sections of this briefing, an examination of the current landscape of HTA in Europe is presented. The insights derived from this research form an essential component of CIRS's ongoing commitment to advancing regulatory and HTA policies and processes.

Health Technology Assessment (HTA) Regulation (EU)

The Regulation (EU) 2021/2282 on HTA applies from 12 January 2025. The aim of this new regulation is to improve access to medicines across the EU by strengthening the quality of HTA. This is done through the work of 4 subgroups that focus on identifying emerging health technologies, developing methodological and procedural guidance, conducting joint clinical assessments (JCAs), and facilitating joint scientific consultations (JSCs). The implementation of JCAs under the HTA Regulation follows a rolling plan, starting in 2025 with oncology products and advanced therapy medicinal products (ATMPs).

CIRS organised a workshop in 2024 that brought together senior representatives from HTA agencies, pharmaceutical companies, payers and patient organisations to discuss the EU HTA Regulation. One of the key recommendations was to develop a metrics framework to evaluate efficiency and inform continuous improvement.

Following this recommendation, the research aims to establish a baseline of the current landscape for oncology products approved by the EMA between 2018 and 2023, assessing HTA outcomes in seven EU countries for comparison with the post-JCA implementation landscape. This briefing analyses the timelines and 1st HTA outcomes of assessed new active substances (NASs) using metrics designed to evaluate the influence of policy changes and support continuous improvement.

METHODOLOGY

The data on individual oncology NASs approved by the EMA between 2018 and 2023 and the timing and HTA outcomes of these products were systematically collected up to and including December 2024. Only the 1st HTA recommendation, derived from the initial assessment, was included in the analysis. The figures below describe the research methodology, designed to enable robust benchmarking between agencies.

Regulatory and HTA process

	Regulatory submission	Regulatory approval	HTA submission	HTA Recommendation
France	Submission to EMA	Approval issued by EU Commission	Date de validation administrative	Publication of Commission de la transparence review
Germany	Submission to EMA	Approval issued by EU Commission	Datum des Auftrags at IQWIG	Publication of Dossierbewertung
Ireland	Submission to EMA	Approval issued by EU Commission	Rapid Review commissioned	Rapid Review completed/ NCPE (full) assessment completed
Netherlands	Submission to EMA	Approval issued by EU Commission	Letter dated by Minister of health to ZIN	Date of Summary of recommendation by ZIN
Poland	Submission to EMA	Approval issued by EU Commission	Order of the Minister of Health publication	Publication of Rekomendacja Prezesa
Portugal	Submission to EMA	Approval issued by EU Commission	Not available from public domain	Data decisão
Sweden	Submission to EMA	Approval issued by EU Commission	Not available from public domain*	Publication of the first released report by TLV

**This information was kindly provided directly by the agency.*

First HTA recommendations: Trichotomous categories

	Positive	Positive with restrictions	*Implication for "positive" or "positive with restrictions"*	Negative
France HAS	Majeur/Important	Modéré ou faible, or mixed reviews for subpopulations	The NHI defines the reimbursement rate accordingly	Insufficient
Germany IQWiG	Considerable/Major added benefit	Minor/non-quantifiable added benefit	G-BA makes the binding resolution based on benefit assessment	Added benefit not proven/less benefit
Ireland NCPE	NAS is considered for reimbursement	NAS is considered for reimbursement with conditions	The HSE considers the NCPE recommendations and make decisions on reimbursement.	NAS not recommended for reimbursement
Netherlands Zorginstituut Nederland	To include	To include + restrictions	Recommendation for inclusion in the national health system	Not to include
Poland	Prezes Agencji rekomenduje	Prezes Agencji rekomenduje+restrictions	Agency's president's recommendation	Prezes Agencji nie rekomenduje
Portugal Infarmed	Deferido	Deferido + restrições	The MoH decides on reimbursement based on the Infarmed report	Indeferido
Sweden TLV	Ngå i läkemedelsförmånerna	Begränsningar	Include in pharmaceutical benefits scheme	Avslår

Note: The terminology used here is based on the individual agency's guidance on the official website. Green outline indicates that drug reimbursement is possible while red outline indicates that drug reimbursement is not possible.

KEY FINDINGS

Between 2018 and 2023, a total of 231 NASs were approved by the EMA, and oncology NASs accounted for 31% of these (n=72) (**Figure 1**). Various flexible regulatory pathways were utilised for the approval of oncology products, with 42% (30/72) of oncology NASs receiving a conditional marketing authorisation (Figure 3).

France (HAS) and Germany (IQWiG) assessed most of the oncology EMA approvals between 2018 and 2023 by the end of 2024 (**Figure 6**). Portugal issued the highest percentage of positive recommendations for the assessed oncology NAS, while France and Germany issued the highest overall number of HTA recommendations (**Figure 7**).

The study highlighted differences in submission strategies to HTAs for oncology NASs, with Poland showing the longest submission gap and rollout time, despite presenting the fastest median HTA review time across all jurisdictions (**Figure 8**).

NASs that underwent the EMA's accelerated pathways generally presented a shorter median time from regulatory submission to HTA recommendation compared to non-accelerated NASs (**Figure 14**); however, no considerable influence was seen in the HTA outcomes (**Figure 15**)

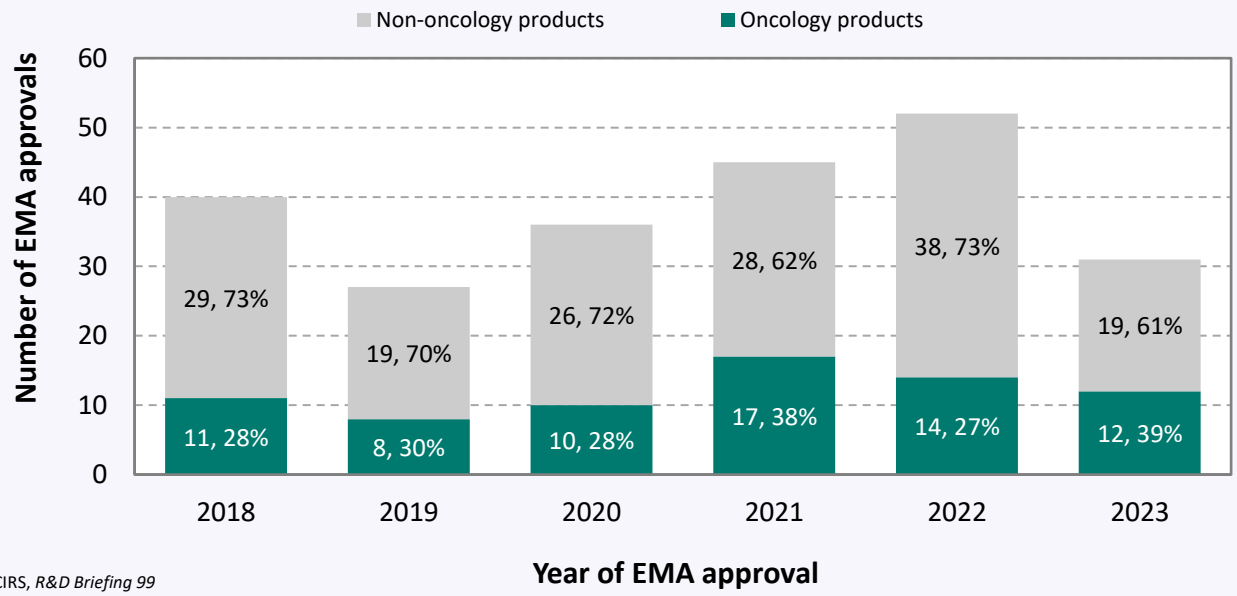
The conditional marketing authorisation, provided to a high proportion of oncology NASs (Figure 3), showed a longer median rollout time for these NASs compared to non-conditional ones (Figure 16).

Seven oncology/ATMP NASs were assessed by all HTA agencies covered in this briefing, all of which received a positive recommendation in France (Table 1). ATMPs in Poland showed a considerably longer rollout time compared to non-ATMPs, driven by a longer submission time (Figure 20).

In January 2028, the EU HTA Regulation (HTAR) will also extend to cover orphan products. Our analysis showed that, among the 28-oncology orphan NASs, half were approved via the conditional marketing authorisation pathway (Figure 21 and Figure 22).

Overview of new drug recommendations

Figure 1. NASs approved by the EMA between 2018 and 2023 (n=231)



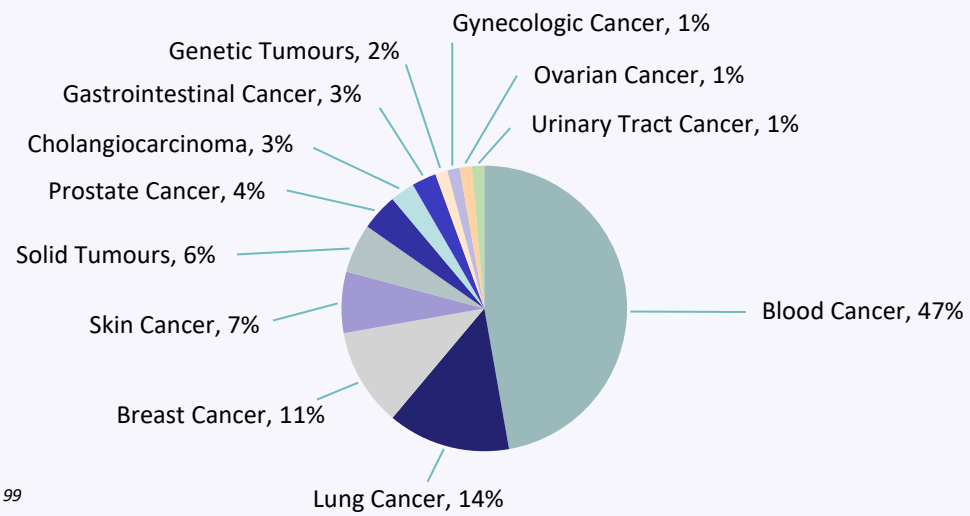
Between 2018 and 2023, a total of 231 NASs were approved by the EMA, 31% of which were oncology NASs.

Oncology drugs represent a high percentage of the total approved NASs and this remains consistent over the years (27%-39%, **Figure 1**). A slight increase can be seen over 2021-2023 compared to 2018-2020.

Among oncology NASs, blood cancer was the therapy area with the highest number of approvals (47%).

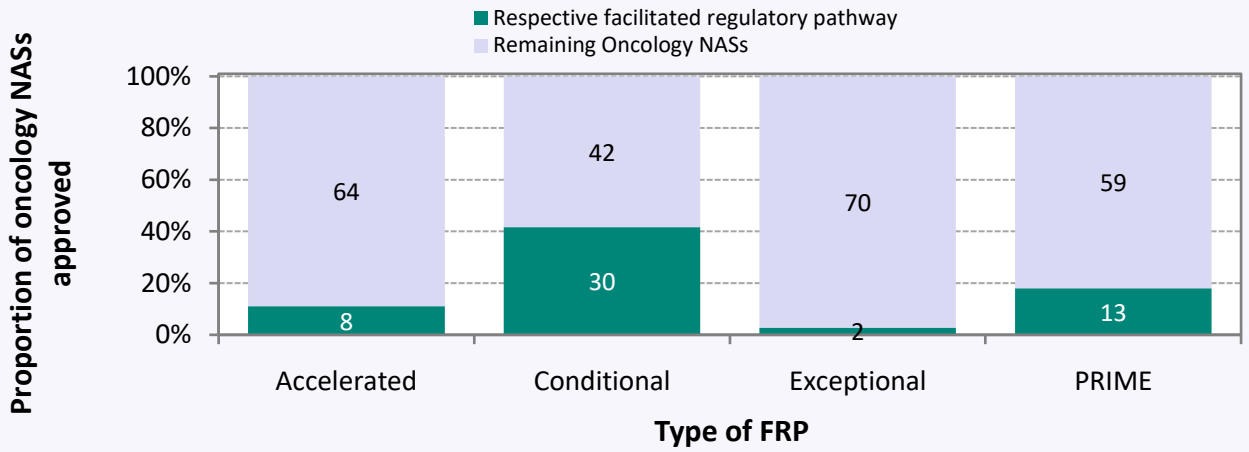
Between 2018 and 2023, 72 oncology products were approved by the EMA. Almost half (47%) of the oncology NASs were approved for blood cancer, while the next largest therapy areas are lung cancer (14%) and breast cancer (11%) (**Figure 2**). The remaining oncology NASs were approved for a considerably wide variety of cancer types in smaller proportions.

Figure 2. Distribution of NASs by cancer type (n=72)
(oncology EMA approvals between 2018–2023)



OVERVIEW OF NEW DRUG RECOMMENDATIONS (CONT.)

Figure 3. Oncology products by facilitated regulatory pathways (oncology EMA approvals between 2018 and 2023, n=72)



Note: Facilitated regulatory pathways are designed to accelerate product development, the submission of market authorisation applications, and regulatory reviews.

A 53% (38/72) of oncology products followed at least one FRP, where conditional approvals were the most utilised for granting market authorisation.

The accelerated and exceptional circumstances pathways, and PRIME designation were used in 11%, 3% and 18% of the oncology products respectively, while a conditional approval was granted in 42% of the oncology NASs (**Figure 3**). The conditional marketing authorisation can be granted by the EMA for medicines on "less comprehensive clinical data than normally required, where the benefit of immediate availability of the medicine outweighs the risk due to the need for additional data". Certain conditions must be met, including that the benefit-risk balance of the medicine is positive. This type of authorisation is valid for a year, which can be either renewed annually or converted into a standard marketing authorisation if the complete data confirm that the benefits continue to outweigh its risks. Approvals of oncology products can undergo multiple pathways simultaneously as shown in **Figure 4**. The PRIME scheme provides developers with early enhanced support to ensure robust data generation, with opportunities for multi-stakeholder discussions including HTA. While the accelerated pathways shortens the time of review of the marketing authorisation application, the exceptional circumstances pathway is provided to medicines for rare diseases or where full efficacy and safety data cannot be collected for different reasons.

10% (7/72) of the EMA-approved oncology NASs between 2018 and 2023 were ATMPs (Figure 5).

The Joint Clinical Assessment (JCA) was implemented in January 2025 for oncology and advanced therapy medicinal products (ATMPs). All 7 ATMPs included in this study were granted a PRIME designation. ATMPs are complex products to develop, manufacture, characterise and test, and the PRIME scheme can support ATMP developers with these aspects.

Figure 4. Oncology products by FRP (n=38) (oncology EMA approvals between 2018 and 2023)

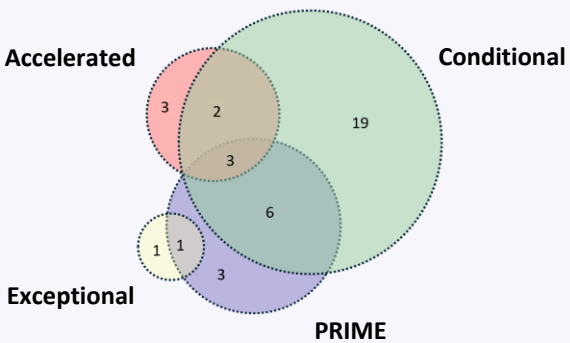
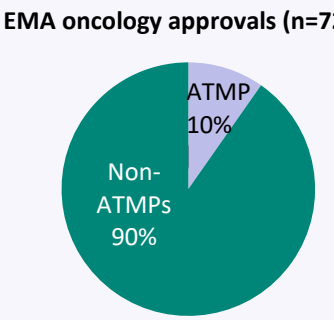
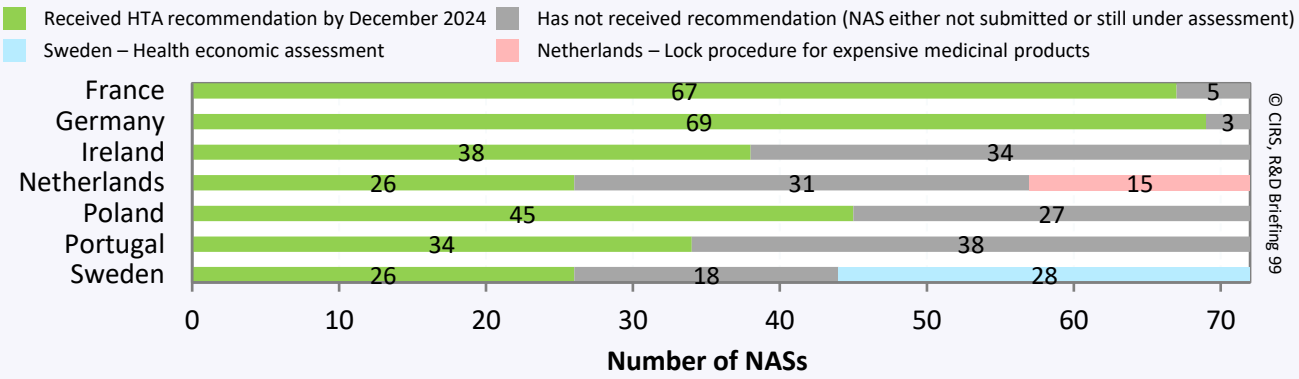


Figure 5. Oncology NASs by ATMP (n=72) (oncology EMA approvals between 2018 and 2023)



FIRST HTA RECOMMENDATION OUTCOMES

Figure 6. Comparison of HTA status across 72 EMA-approved oncology NASs (approvals between 2018 and 2023)

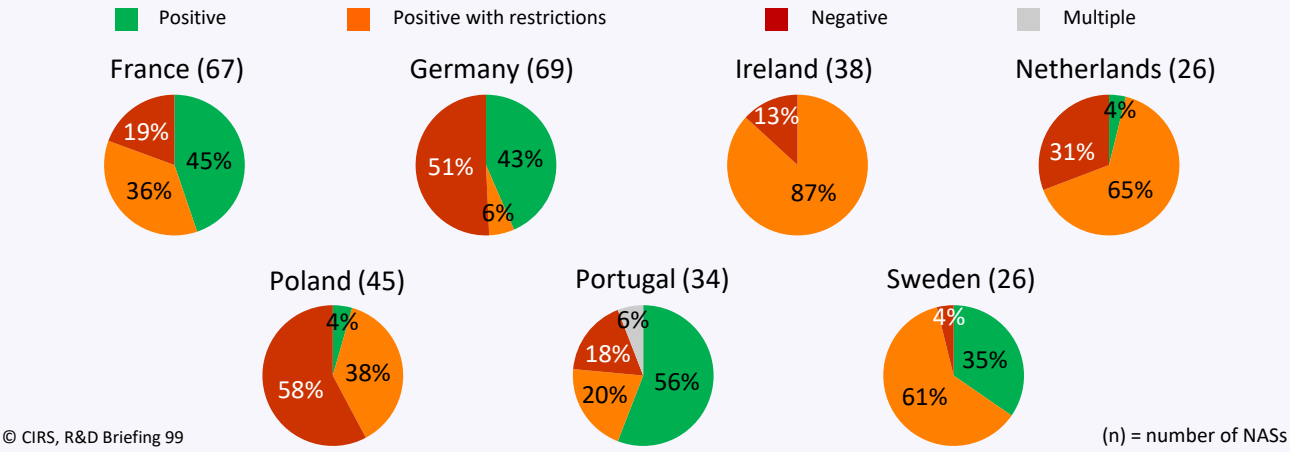


Note: The "has not received a recommendation" category does not imply that the products are unavailable to patients, as they may be accessible through alternative pathways. For example, ZIN (Netherlands) and TLV (Sweden) do not issue recommendations for inpatient drugs, only for outpatient medicines.

France (HAS) and Germany (IQWIG) assessed most of the oncology products approved by EMA between 2018 and 2023 (93% and 96%, respectively) by the end of 2024.

Figure 6 illustrates the number of recommendations provided by these seven agencies for the 72 oncology NASs approved between 2018 and 2023. The number of HTA recommendations across jurisdictions is related to multiple factors such as the company submission, the assessment time by HTA agencies, and the scope of the HTA agencies. For example, in Netherlands and Sweden, only outpatient drugs are assessed by ZIN and TLV. The lock procedure for expensive medicinal products was introduced for ZIN (Netherlands) as these medicines are considered "extremely expensive" by the Ministry of Health, Welfare and Sport (VWS) and are maintained outside the basic health insurance package temporarily. For inpatient products, TLV (Sweden) does not provide a recommendation as these fall outside of their remit, however, they still produce health economic assessment reports for these products to guide decision making at the regional level. These two categories were not included in the remaining analyses (Fig 7 onwards).

Figure 7. Outcome of 1st HTA recommendations (oncology EMA approvals between 2018 and 2023 that received an HTA recommendation)



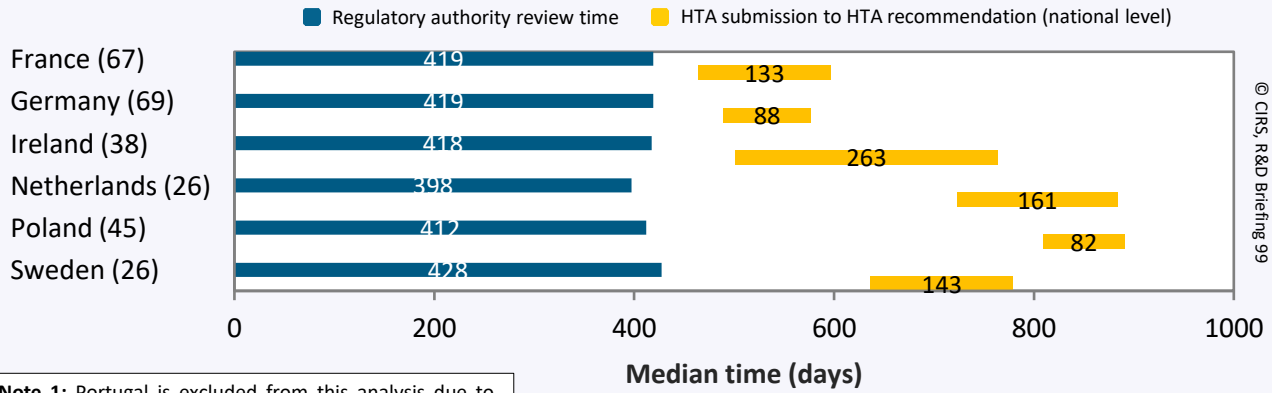
Portugal had the highest proportion of positive HTA recommendations (without restrictions) at the national level.

To further explore the recommendations provided by the seven studied jurisdictions, **Figure 7** presents the outcomes of the recommendations shown in **Figure 6**. In Portugal more than half of the oncology products were issued a positive recommendation (without restrictions), while in Ireland none of the assessed products received a positive recommendation (without restrictions). Nevertheless, Ireland had the second lowest percentage of negative recommendations (13%), only after Sweden (4%). It is important to note that products that receive a negative HTA recommendation could still get reimbursed in some jurisdictions, e.g. in Ireland, the final reimbursement decision is made by the Health Service Executive, considering NCPE's recommendation among other factors.

Since the introduction of the Early Access pathway in France in 2021, 19 of the assessed oncology NASs were granted Early Access (data not shown). The Early Access pathway enables early availability and reimbursement of medicinal products indicated for severe, rare, or incapacitating diseases before either a marketing authorisation is granted or an HTA recommendation is issued.

OVERALL TIMELINES

Figure 8. Timing from EMA submission to 1st HTA recommendation (oncology EMA approvals between 2018 and 2023 with an HTA recommendation)



(n) = number of NASs

Note 1: Portugal is excluded from this analysis due to unavailable HTA submission dates in the public domain.

Note 2: For Ireland, both rapid and full reviews are included in this analysis. In addition, the HTA review for Ireland time is calculated as (Rapid review completed - Rapid review commissioned) + (NCPE assessment completed - Full submission received from applicant)

Poland exhibited the longest submission gap but the fastest median HTA review time across all jurisdictions.

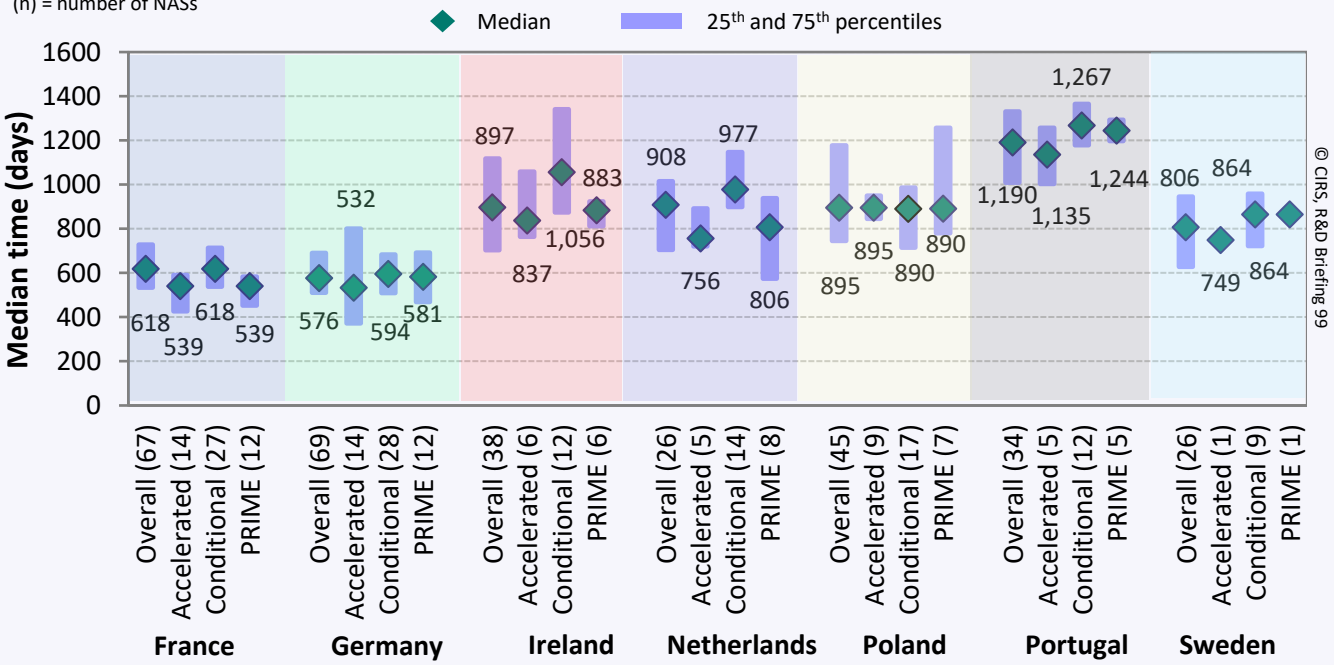
Germany had the 2nd fastest HTA review time (after Poland). However, due to a shorter submission gap than Poland, it presented the shortest overall rollout time (**Figure 8**). Poland had the longest rollout time, driven by the long submission gap.

The rollout time was analysed in more detail to understand the impact of FRPs (**Figure 9**).

Conditionally approved products showed a longer rollout, apart from Poland where it was slightly shorter for conditional compared to the overall rollout time. Ireland and Poland exhibited higher variability than the rest of the jurisdictions. In the case of Ireland, this may be explained by their two types of HTA reviews: rapid reviews (RR) and full HTAs (FR). Rapid reviews are used to assess new medicines to determine if they require a more comprehensive evaluation (full HTA) but if not needed, the RR provides a faster recommendation on reimbursement.

Figure 9. Variation of time from EMA submission to 1st HTA recommendation by FRP (oncology EMA approvals between 2018 and 2023 with an HTA recommendation)

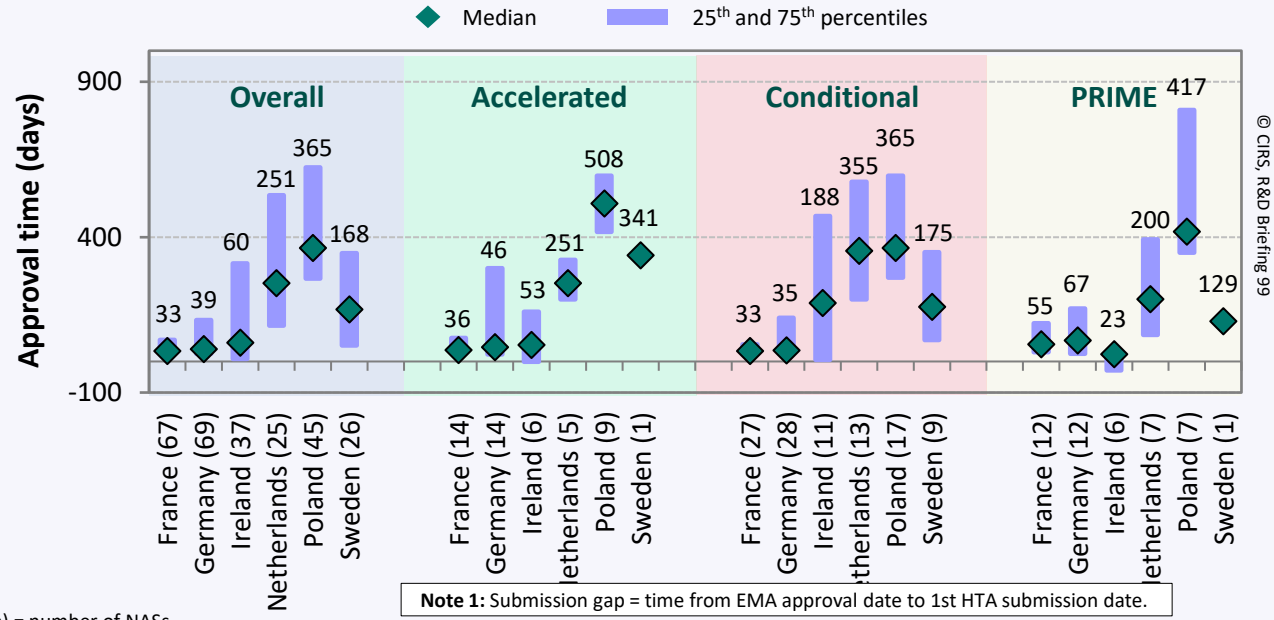
(n) = number of NASs



Note: For Ireland, both rapid and full reviews are included in this analysis In addition, the HTA review for Ireland time is calculated as (Rapid review completed - Rapid review commissioned) + (NCPE assessment completed - Full submission received from applicant).

SUBMISSION STRATEGY

Figure 10. Submission gap by FRP
(oncology EMA approvals between 2018 and 2023 with an HTA recommendation)



(n) = number of NASs

Note 1: Submission gap = time from EMA approval date to 1st HTA submission date.

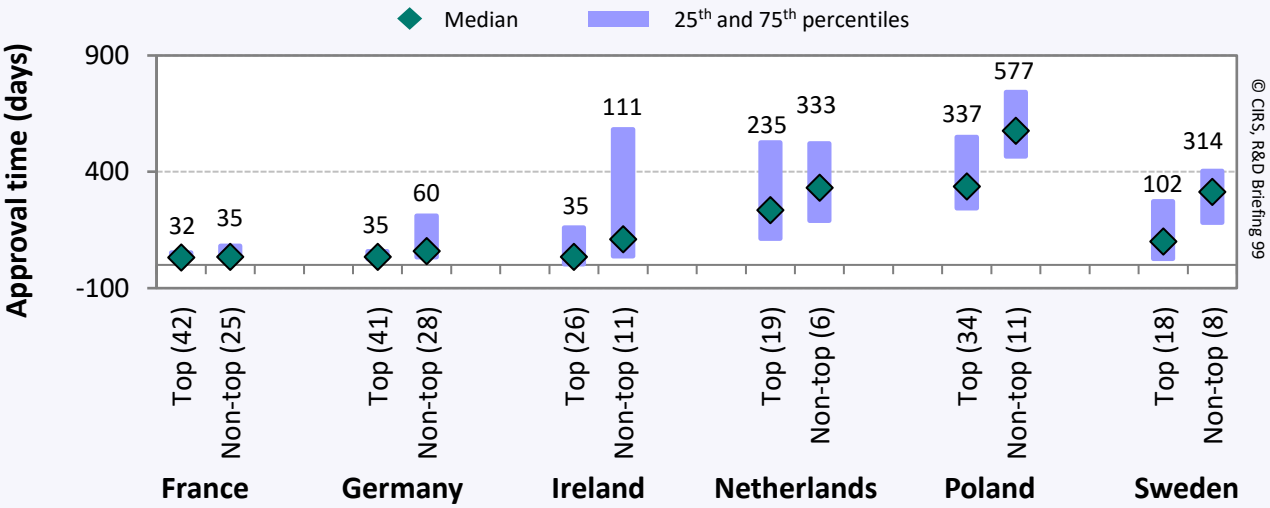
Note 2: Portugal was excluded due to unavailable HTA submission dates in the public domain.

France and Germany showed the shortest submission gap by FRP, except for PRIME designated products.

Company submission strategies were examined in more detail (**Figure 10** and **Figure 11**). Poland had the longest submission gap overall and across all FRPs. PRIME oncology products in Ireland showed the lowest submission gap which ranged from -29 days (25th percentile) to 28 days (75th percentile). This is due to two PRIME products being submitted in parallel with the regulatory review.

The submission gap was further analysed in terms of the company size, defined by R&D spending (**Figure 11**). Top companies showed shorter median submission gaps than companies with lower R&D spending, which could potentially be explained by the better capacity and resource for local affiliates.

Figure 11. Submission gap by company R&D spending
(oncology EMA approvals between 2018 and 2023 with an HTA recommendation)



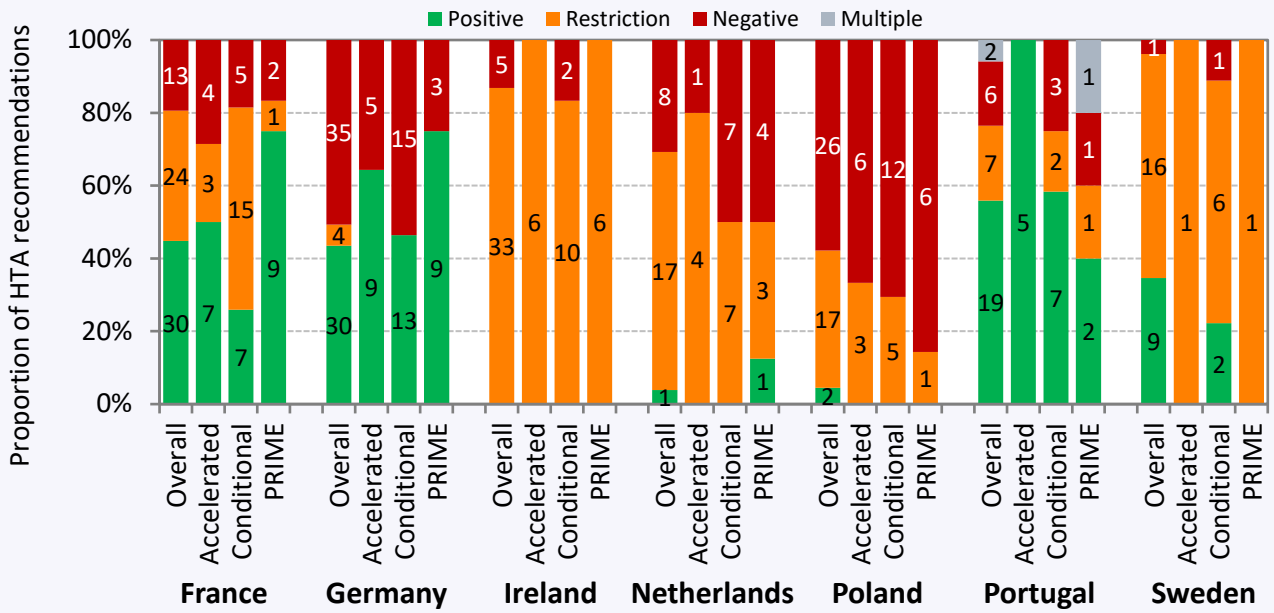
(n) = number of NASs

Note 1: Portugal was excluded due to unavailable HTA submission dates in the public domain.

Note 2: Top company refers to pharmaceutical companies with R&D spending >3 billion USD in 2021. Non-top companies had and R&D spending <3 billion USD in 2021.

Characteristics: Facilitated Regulatory Pathway

Figure 12. Outcome of 1st HTA recommendation by FRP
(oncology EMA approvals between 2018 and 2023 with an HTA recommendation)

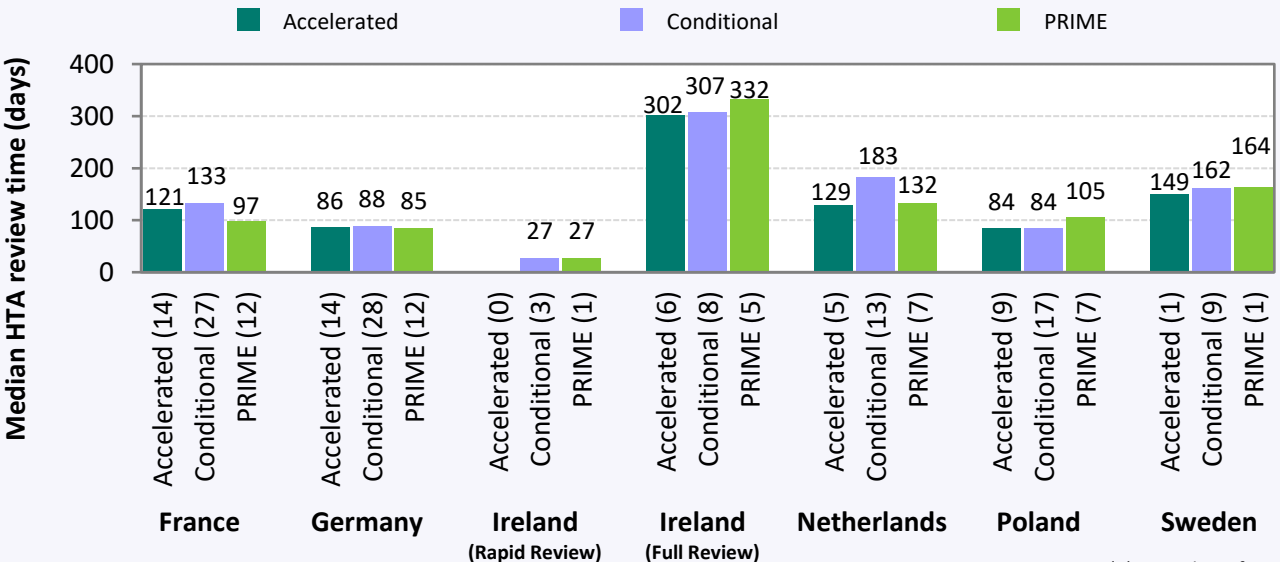


HTA outcomes of oncology NASs were assessed by comparing different FRPs to the overall outcomes, revealing a lack of consistency across jurisdictions.

FRPs have been increasingly used by regulatory agencies to accelerate submission, review and approval of medicines where there is an unmet medical need (CIRS R&D Briefing 93). **Figure 12** illustrates the proportions of HTA outcomes by FRPs to assess whether FRPs may be associated with HTA outcomes. Germany and Ireland showed slightly better outcomes for FRPs than the overall. Contrarily, Poland presented a reduction in the proportion of positive and positive with restrictions outcomes (42% for overall, 33% for accelerated, 29% for conditional, and 14% for PRIME).

This descriptive analysis explores whether HTA review times differ for products that underwent FRPs, such as accelerated approval, conditional marketing authorisation, or PRIME designation. **Figure 13** presents HTA review times across countries for these products. In the case of Ireland, rapid reviews (RR) and full HTAs (FR) are shown separately. Review times appeared relatively consistent across countries and FRP types. This observation suggests that HTA timelines may remain unaffected.

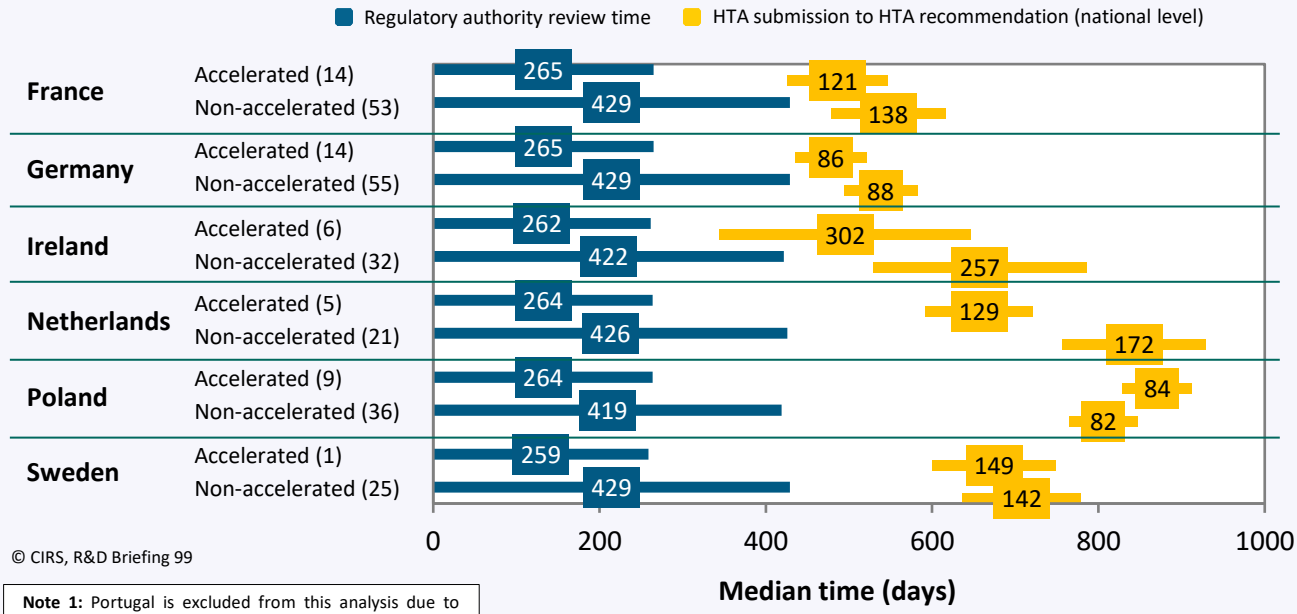
Figure 13. Comparison of median HTA review time by FRP
(oncology EMA approvals between 2018 and 2023 with an HTA recommendation)



(n) = number of NASs

CHARACTERISTICS: ACCELERATED REGULATORY APPROVAL

Figure 14. Breakdown of rollout time by accelerated pathway (oncology EMA approvals between 2018 and 2023 with an HTA recommendation)



Note 1: Portugal is excluded from this analysis due to unavailable HTA submission dates in the public domain.

Note 2: For Ireland, both rapid and full reviews are included in this analysis. In addition, the HTA review for Ireland time is calculated as (Rapid review completed - Rapid review commissioned) + (NCPE assessment completed - Full submission received from applicant)

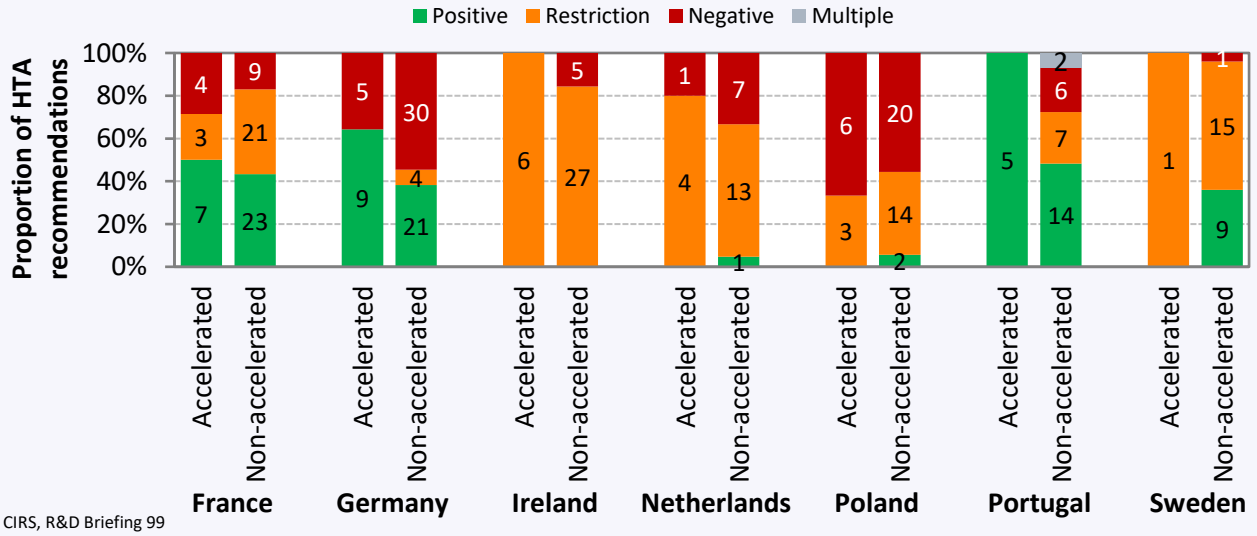
(n) = number of NASs

Generally, NASs approved through the accelerated regulatory pathway exhibited a shorter median rollout time, despite varied HTA review times.

The rollout time of accelerated products was shorter than non-accelerated products in most countries (except Poland), which are mainly driven by the shorter regulatory review time for accelerated products (**Figure 14**). An additional analysis on the submission strategy showed that in all countries - apart from Ireland and Netherlands – the median time between the regulatory approval and the HTA submission was longer for accelerated compared to non-accelerated products: 36 vs 33 days in France, 46 vs 39 days in Germany, 53 vs 60 days in Ireland, 251 vs 273 days in Netherlands, 508 vs 334 days in Poland, 341 vs 160 days in Sweden.

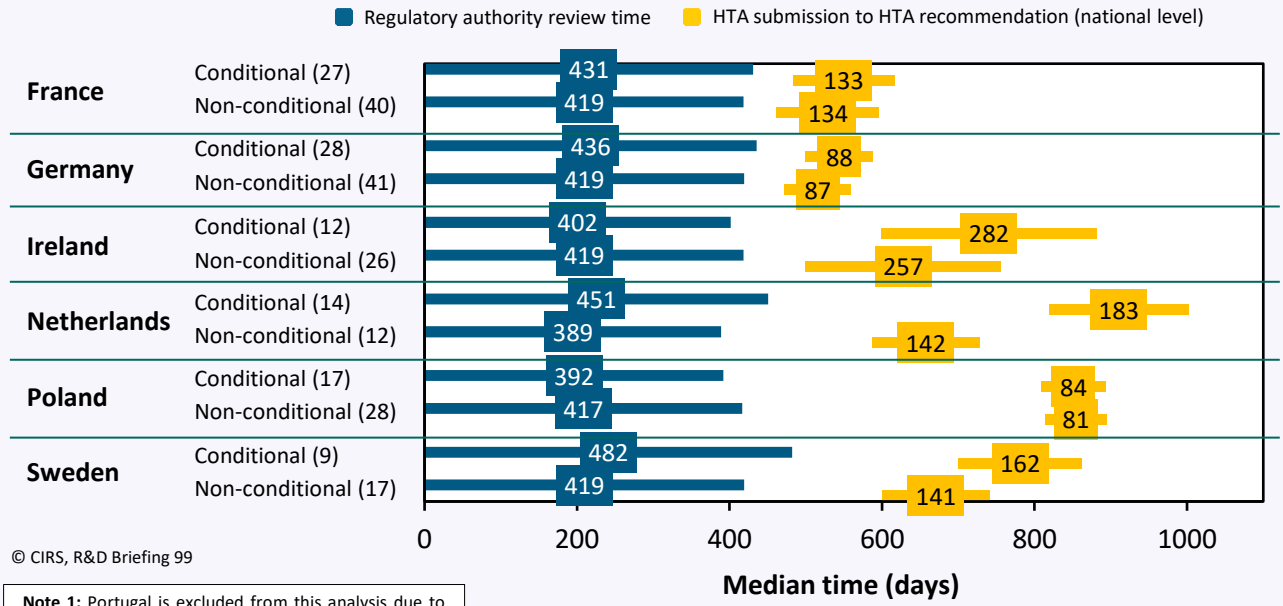
The proportion of positive and positive with restriction outcomes was higher for accelerated products in all countries except France and Poland (**Figure 15**).

Figure 15. Outcome of 1st HTA recommendation by accelerated pathway (oncology EMA approvals between 2018 and 2023 with an HTA recommendation)



CHARACTERISTICS: CONDITIONAL REGULATORY APPROVAL

Figure 16. Breakdown of rollout time by conditional pathway (oncology EMA approvals between 2018 and 2023 with an HTA recommendation)



Note 1: Portugal is excluded from this analysis due to unavailable HTA submission dates in the public domain.

Note 2: For Ireland, both rapid and full reviews are included in this analysis. In addition, the HTA review for Ireland time is calculated as (Rapid review completed - Rapid review commissioned) + (NCPE assessment completed - Full submission received from Applicant)

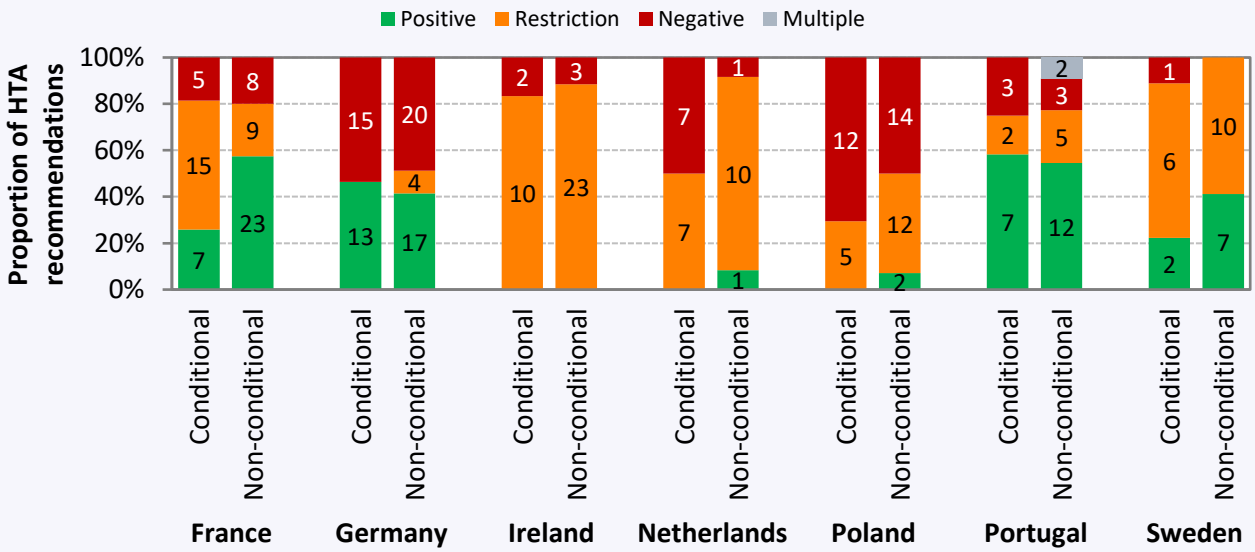
(n) = number of NASs

Oncology products approved through a conditional regulatory pathway presented a longer median rollout time than non-conditional oncology products.

Receiving a conditional approval showed a longer EMA regulatory review and HTA review in most jurisdictions (**Figure 16**). The submission gap on the other hand was not always longer for conditional compared to non-conditional in all jurisdictions: 33 vs 34 days in France, 35 vs 42 days in Germany, 188 vs 54 days in Ireland, 355 vs 134 days in Netherlands, 365 vs 377 days in Poland, 175 vs 160 days in Sweden.

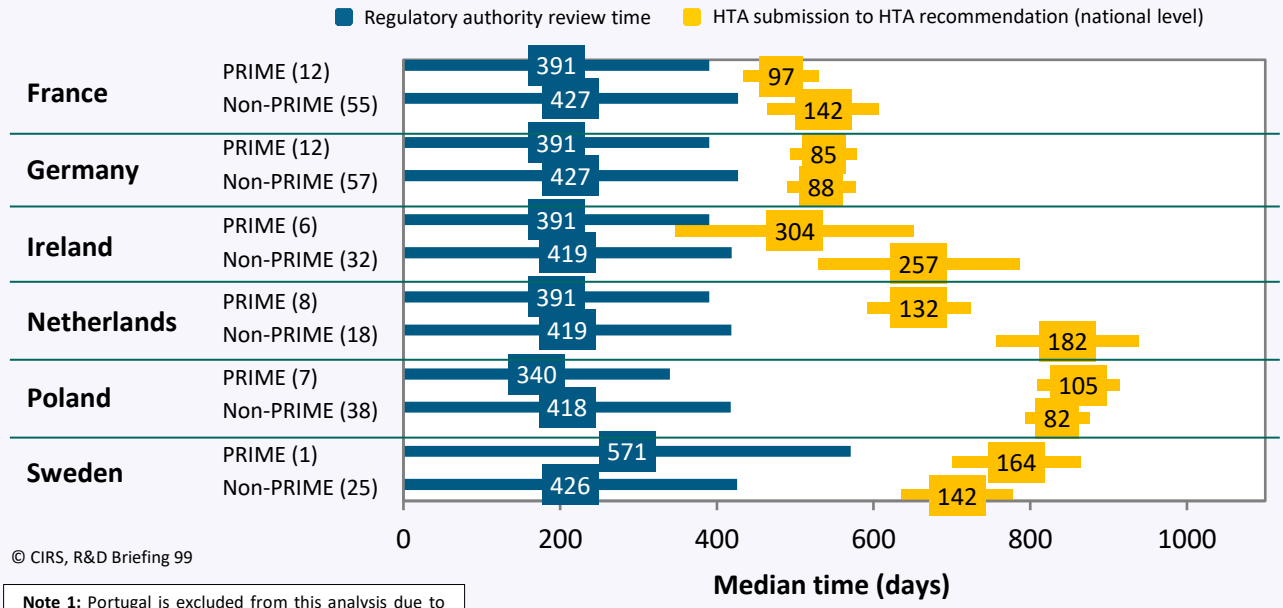
The data in **Figure 17** show that the proportions of HTA outcomes in conditional versus non-conditional NASs varies between different jurisdictions. However, conditional products showed a higher percentage of negative outcomes in all countries apart from France.

Figure 17. Outcome of 1st HTA recommendation by conditional pathway (oncology EMA approvals between 2018 and 2023 with an HTA recommendation)



CHARACTERISTICS: PRIME DESIGNATION

Figure 18. Breakdown of rollout time by PRIME designation (oncology EMA approvals between 2018 and 2023 with an HTA recommendation)



Note 1: Portugal is excluded from this analysis due to unavailable HTA submission dates in the public domain.

Note 2: For Ireland, both rapid and full reviews are included in this analysis. In addition, the HTA review for Ireland time is calculated as (Rapid review completed - Rapid review commissioned) + (NCPE assessment completed - Full submission received from applicant)

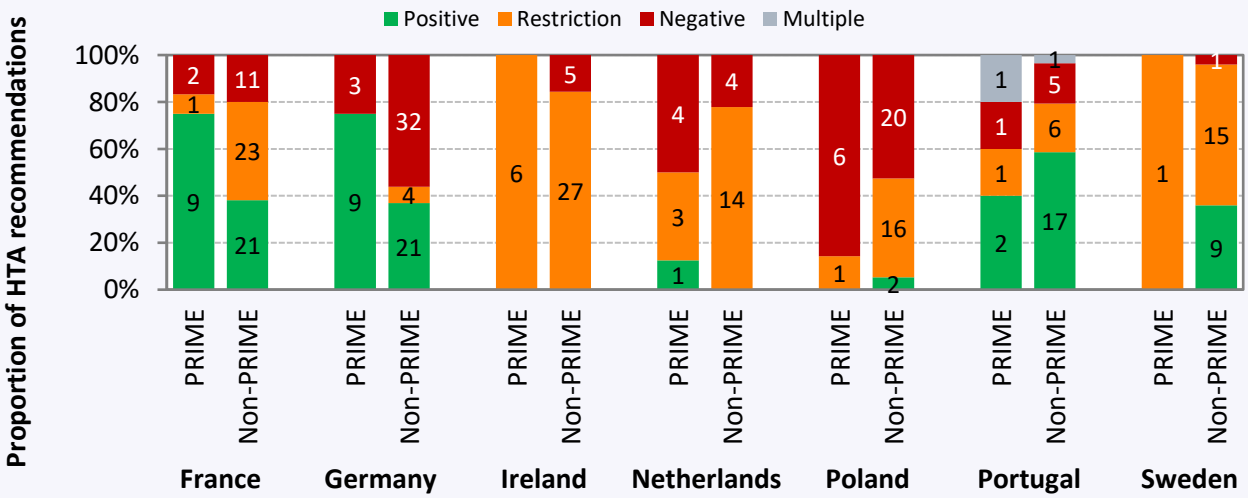
(n) = number of NASs

A shorter rollout time is not consistently shown for PRIME products compared to non-PRIME oncology NASs.

The EMA introduced the PRIME scheme to support the development of medicines that target unmet medical needs early on through scientific advice and to expedite the EMA evaluation process of these medicines. This was achieved in most jurisdictions for oncology products as seen in **Figure 18**. The HTA review time was also shorter in France, Germany and Netherlands, however, this was not observed in other jurisdictions. Contrarily, France and Germany showed a longer submission gap for PRIME versus non-PRIME products: 55 vs 33 days in France, 67 vs 39 days in Germany, 23 vs 65 days in Ireland, 200 vs 319 days in Netherlands, 417 vs 347 days in Poland, and 129 and 175 days in Sweden.

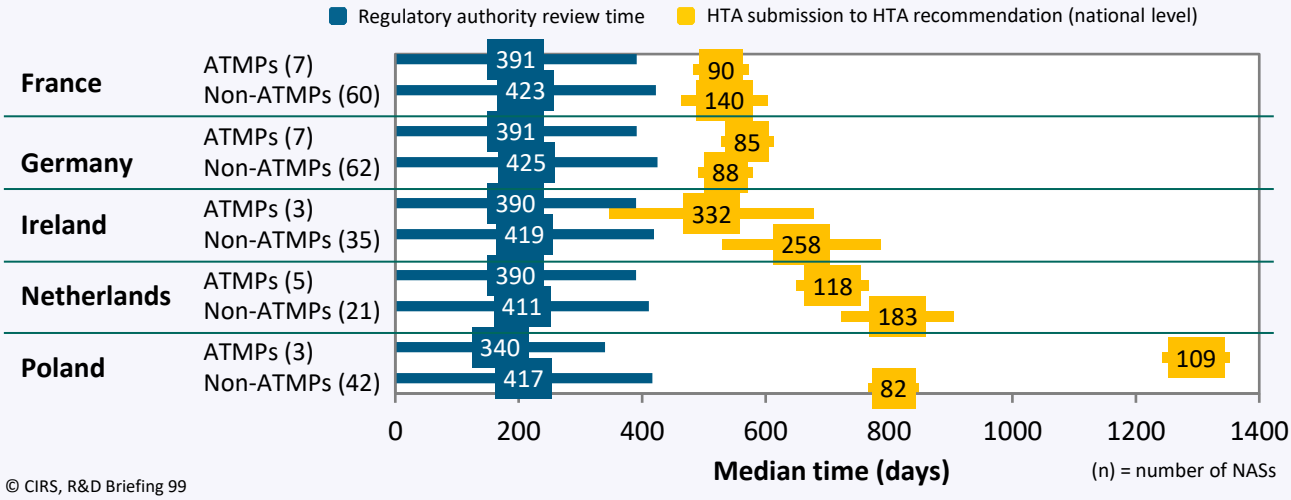
Regarding the outcome of the 1st recommendation for PRIME products, no clear relation was found between the regulatory pathway and the HTA outcome **(Figure 19)**.

Figure 19. Outcome of 1st HTA recommendation by PRIME designation (oncology EMA approvals between 2018 and 2023 with an HTA recommendation)



CHARACTERISTICS: ATMPS

Figure 20. Breakdown of rollout time by ATMPs (oncology EMA approvals between 2018–2023 that received an HTA recommendation)



Note 1: Portugal is excluded from this analysis due to unavailable HTA submission dates in the public domain. Sweden was also excluded as no ATMPs were reviewed by TLV.

Note 2: For Ireland, both rapid and full reviews are included in this analysis. In addition, the HTA review for Ireland time is calculated as (Rapid review completed - Rapid review commissioned) + (NCPE assessment completed - Full submission received from applicant)

ATMPs in Poland showed a considerably longer median rollout time compared to non-ATMP NASs, driven by a longer submission gap.

ATMPs showed a shorter median regulatory review time than non-ATMPs (**Figure 20**). A shorter median HTA review time for ATMPs than non-ATMPs was also observed in most jurisdictions (France, Germany, Netherlands). In Ireland, the HTA review of one of the ATMPs was conducted in parallel with the regulatory review.

France provided positive recommendations to all oncology ATMPs approved between 2018 and 2023 (Table 1).

In Ireland, the restrictions were related to cost-effectiveness and these three products were reimbursed following confidential price negotiations. Netherlands has placed two of the ATMPs in the lock procedure as they were deemed extremely expensive. In Sweden's case, the lack of recommendations is explained by TLV not being responsible for issuing recommendations for inpatient medicines.

Table 1. ATMPs products assessed by HTA (n=7) (oncology EMA approvals between 2018 and 2023 with an HTA recommendation)

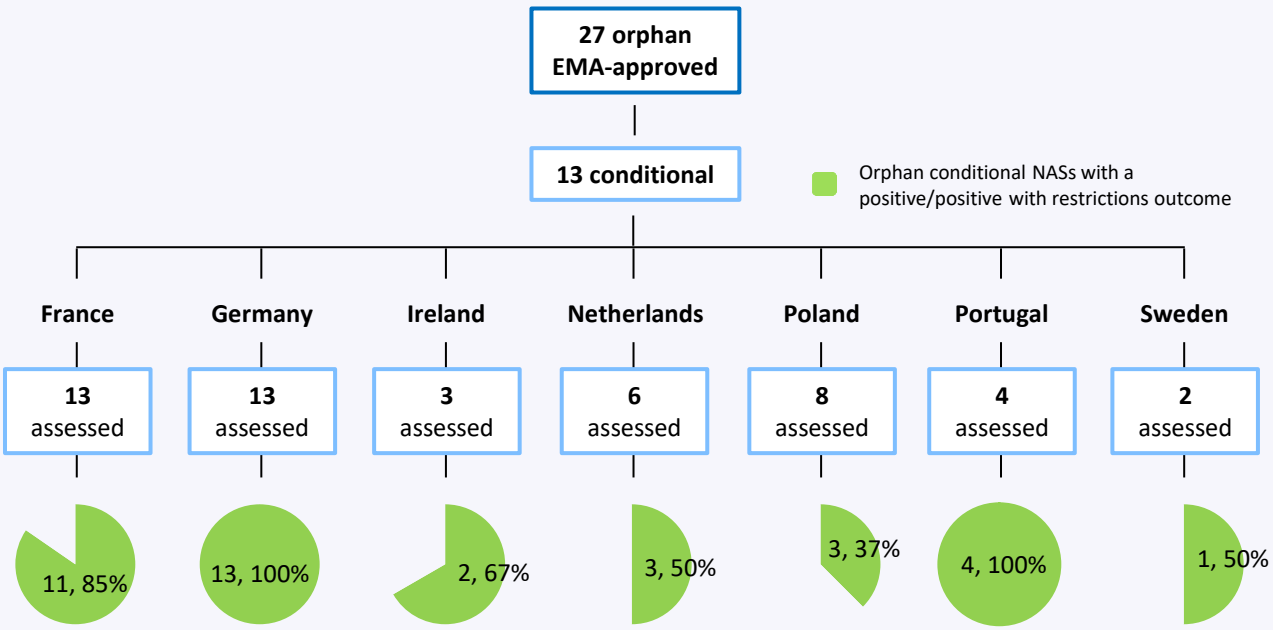
Positive | Positive with restrictions | Negative | Multiple

Generic name	Regulatory approval year	France	Germany	Ireland	Netherlands	Poland	Portugal	Sweden
axicabtagene ciloleucel	2018							Health economic assessment
tisagenlecleucel	2018							Health economic assessment
brexucabtagene autoleucel	2020			No HTA recommendation				Health economic assessment
idecabtagene vicleucel	2021			No HTA recommendation	Lock procedure	No HTA recommendation	No HTA recommendation	Health economic assessment
ciltacabtagene autoleucel	2022					No HTA recommendation	No HTA recommendation	Health economic assessment
lisocabtagene maraleucel	2022			No HTA recommendation		No HTA recommendation	No HTA recommendation	Health economic assessment
tabelecleucel	2022			No HTA recommendation	Lock procedure	No HTA recommendation	No HTA recommendation	No HTA recommendation

Note: "no HTA recommendation" means there was no recommendation issued up until December 2024. A recommendation could have been issued in 2025 but this is out of scope for this briefing.

CHARACTERISTICS: ORPHAN

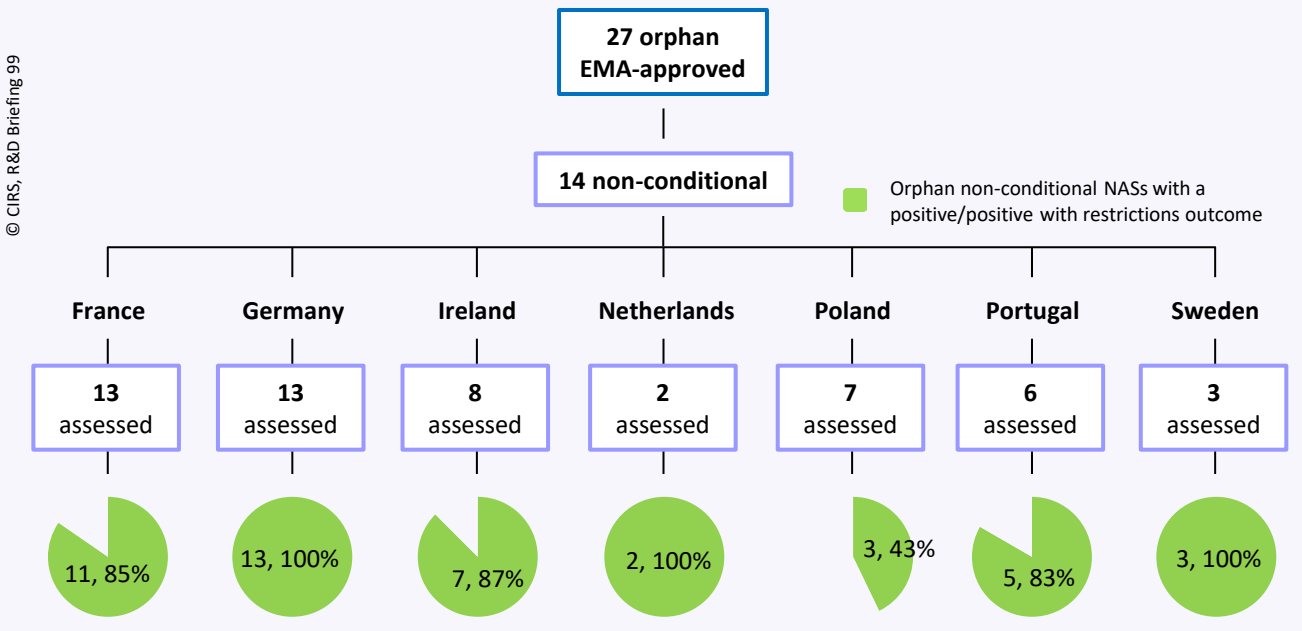
Figure 21. 1st outcome of orphan products by conditional pathway (oncology EMA approvals between 2018–2023)



Almost half of the oncology orphan products were approved through the conditional regulatory pathway.

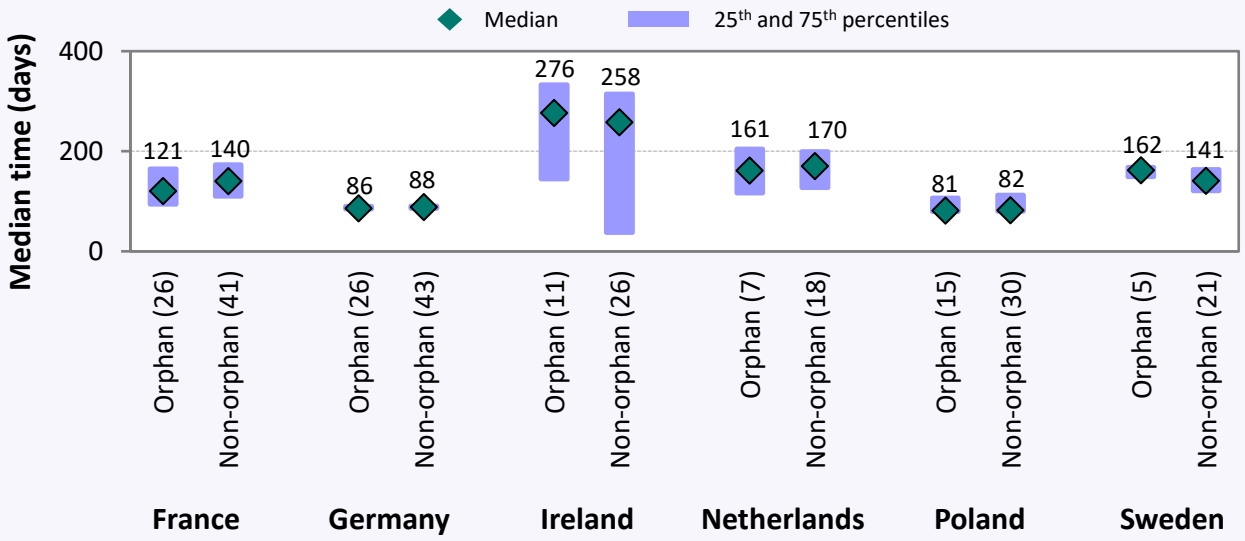
A total number of 27 oncology NASs were granted with orphan designation, of which 13 (48%) were conditional approvals. In **Figures 21** and **22**, we explored the 1st HTA outcome for orphan oncology NASs that were approved underwent conditional vs non-conditional pathways. Out of the products that were assessed by the corresponding agencies, a similar or slightly higher percentage received a positive or positive with restrictions outcome if they had not received a conditional approval, except in Portugal. This could be related to conditional approvals being granted to medicines with less comprehensive clinical data, which could reduce the likelihood of an optimal outcome. The 100% positive outcomes in Germany are explained by the fact that orphan drugs have a privilege status which exempts them from the regular benefit assessment procedure and leads to an automatic assumption of added benefit.

Figure 22. 1st outcome of orphan products by conditional pathway (oncology EMA approvals between 2018–2023)



CHARACTERISTICS: ORPHAN (CONT.)

Figure 23. Variation of HTA review time by orphan designation (oncology EMA approvals between 2018–2023 that received an HTA recommendation)



Note 1: Portugal is excluded from this analysis due to unavailable HTA submission dates in the public domain.

Note 2: For Ireland, both rapid and full reviews are included in this analysis. In addition, the HTA review for Ireland time is calculated as (Rapid review completed - Rapid review commissioned) + (NCPE assessment completed - Full submission received from applicant)

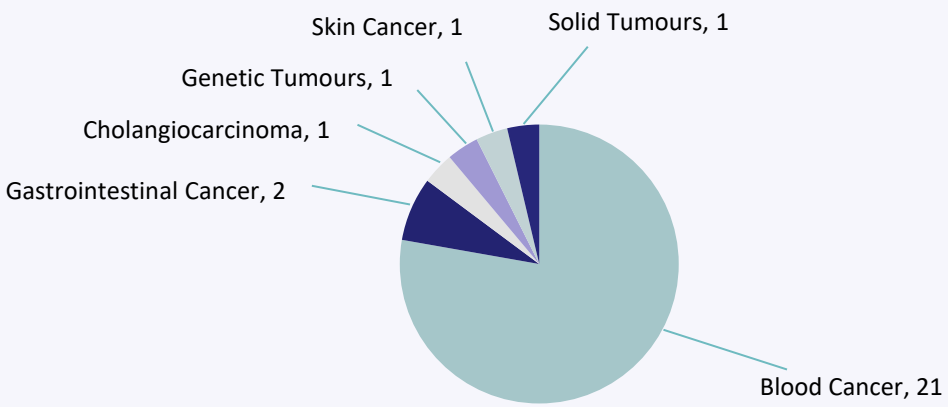
(n) = number of NASs

The median HTA review time was similar for orphan designated and non-orphan designated oncology NASs between 2018 and 2023.

There is low variability in the median HTA review time in most jurisdictions apart from Ireland (**Figure 23**). In Ireland, this is due to both rapid reviews and full HTAs being included in this analysis.

Most of the oncology products granted orphan designation were indicated for the treatment of blood cancer (72%) (Figure 24).

Figure 24. Distribution of orphan-designated NASs (n=27) by cancer type (oncology EMA approvals between 2018–2023 with at least one HTA recommendation)



DEFINITIONS

Advanced therapy medicinal products (ATMPs)

Advanced therapy medicinal products (ATMPs) are medicines for human use that are based on genes, tissues or cells.

Early Access – HAS (France)

Since 2021, HAS evaluates and authorises medicines that are requested for coverage under the "early access" provision. This is a mechanism that allows patients in a therapeutic impasse to benefit, on an exceptional and temporary basis, from certain drugs not authorised for a specific therapeutic indication. It applies to drugs either awaiting reimbursement approval or lacking marketing authorisation. The following four conditions must be met:

1. The drug must be intended to treat serious, rare, or disabling diseases.
2. No appropriate treatment must be available.
3. Implementation of the treatment cannot be postponed.
4. The medicinal product must be presumed to be innovative, especially in comparison to a possibly clinically relevant comparator.

Health technology assessment (HTA)

For the purpose of this project, HTA refers to the assessment and appraisal of pharmaceuticals prior to reimbursement. The HTA process includes clinical assessment, economic assessment and an appraisal that results in either a coverage recommendation or recommendation.

HTA review time

Time (calendar days) calculated from the date of submission to the date of recommendation by the HTA agency. Note: The HTA recommendation refers to the recommendation at national level.

New active substance (NAS)

A chemical, biological, biotechnology or radiopharmaceutical substance that has not been previously available for therapeutic use in humans and is destined to be made available as a 'prescription-only medicine', to be used for the cure, alleviation, treatment, prevention or in vivo diagnosis of diseases in humans; the term NAS also includes:

- An isomer, mixture of isomers, a complex or derivative or salt of a chemical substance previously available as a medicinal product but differing in properties with regard to safety and efficacy from that substance previously available.
- A biological or biotech substance previously available as a medicinal product, but differing in molecular structure, nature of source material or manufacturing process and which will require clinical investigation.
- A radiopharmaceutical substance that is a radionuclide or a ligand not previously available as a medicinal product. Alternatively, the coupling mechanism linking the molecule and the radionuclide has not been previously available.
- Applications that are excluded from the study:
    - Non-oncology products
    - Vaccines
    - Any other application, where new clinical data were submitted
    - Generic applications
    - Those applications where a completely new dossier was submitted from a new company for the same indications as already approved for another company
    - Applications for a new or additional name, or a change of name, for an existing compound (i.e., a 'cloned' application)

Oncology drugs

In this Briefing, oncology drugs refers to drugs with ACT codes L, V09, or V10, which were approved for a type of cancer. The indication was obtained from the corresponding European Public Assessment Reports (EPARs).

Orphan drugs

Medicines intended for use against a rare condition that are provided the orphan designation by the EMA. The medicine must fulfil certain criteria for designation as an orphan medicine so that it can benefit from incentive such as protection from competition once on the market.

Parallel review

Pharmaceutical companies submit evidence to the regulatory agency that prove the efficacy, safety, quality of the product. However, during the regulatory review process, companies submit dossiers to HTA bodies so that the two review steps can occur in parallel. Following the regulatory approval, HTA recommendation will be provided to companies for drug reimbursement. In this report, a drug is identified as parallel if HTA recommendation is earlier than regulatory approval.

Regulatory review time

Time (calendar days) calculated from the date of submission to the date of approval by the agency; this time includes agency and company time. Note: The EMA approval time includes the EU Commission time.

Rollout time

Date of submission at the regulatory agency to the date of HTA recommendation at the target jurisdiction (calendar days).

DEFINITIONS (CONT.)

Sequential review

A regulatory review is conducted first to determine the benefit-risk profile of a new medicine, followed by the HTA review to assess the value of the medicine for a reimbursement decision. The regulatory-HTA sequence is seen at a national level in many countries, and also at a super-national level in Europe where a centralised regulatory decision made by the European Medicines Agency is followed by jurisdictional HTA recommendations by member states.

Top company

Pharmaceutical company with R&D spending >3 billion USD in 2021 (Reference).

EMA Facilitated Regulatory Pathways

Table 2: Facilitated regulatory pathways

TYPE OF FRP	WHAT IS IT?	ADVANTAGE
EMA Accelerated Assessment	A process designed to expedite products of major interest in terms of public health and therapeutic innovation	• Committee for Medicinal Products for Human Use (CHMP) opinion shortened from 210 days to 150 days
EMA Conditional Approval	Regulation allowing drugs fulfilling unmet medical need for severe, life-threatening or rare diseases to be approved with limited clinical safety or efficacy data, provided a positive benefit-risk balance	• Conditional approval is granted before all data are available (valid for one year, on a renewable basis; once pending studies are provided, it can become a "normal" marketing authorisation)
EMA Exceptional Circumstances	Regulation allowing drugs fulfilling unmet medical need for severe, life-threatening or rare diseases to be approved without comprehensive efficacy and safety data	• Conditional approval is granted before all data are available (reviewed annually to re-assess the risk-benefit balance)
EMA PRIME (Priority Medicines)	A scheme to enhance support for the development of medicines that target an unmet medical need. It is based on enhanced interaction and early dialogue with developers of promising medicines, to optimise development and speed evaluation.	• Early dialogue with EMA (appointed rapporteur) • Provision of scientific advice, involving additional stakeholders (e.g. HTA) • Dedicated point of contact from EMA • Option of Accelerated Assessment

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About CIRS

The Centre for Innovation in Regulatory Science (CIRS) is a neutral, independent UK-based subsidiary of Clarivate plc. Its mission is to maintain a leadership role in identifying and applying scientific principles for the purpose of advancing regulatory and health technology assessment (HTA) policies and processes.

CIRS provides an international forum for industry, regulators, HTA and other healthcare stakeholders to meet, debate and develop regulatory and reimbursement policy. It is governed and operated by Clarivate for the sole support of its members' activities. The organisation has its own dedicated management and advisory boards, and its funding is derived from membership dues, related activities, and grants.

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