iPAAC
INNOVATIVE PARTNERSHIP
FOR ACTION AGAINST CANCER

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Horizon scanning systems applied for Cancer control in Europe

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Abbreviations

CAR-T	Chimeric Antigen Receptor-T
CAV	Clinical Added Value
EAA	Early Awareness and Alert
EFPIA	European Federation of Pharmaceutical Industries and Associations
EMA	European Medicine Agency
ESMO	European Society for Medical Oncology
EU	European Union
EUnetHTA	European Network for Health Technology Assessment
FDA	Food and Drug Administration
HAS	Haute Autorité de santé (French HTA agency)
HOPE	European Hospital and Healthcare Federation
HS	Horizon Scanning
HSS	Horizon Scanning Systems
HTA	Health Technology Assessment
ICMRA	International Coalition of Medicines Regulatory Authorities
IHSI	International Horizon Scanning Initiative
INCa	French National Cancer Institute
iPAAC	Innovative Partnership for Action Against Cancer
KCE	Belgian Health Care Knowledge Center
LEEM	Les Entreprises du Médicament (French pharmaceutical industry network)
MA	Marketing Authorization
MCBS	Magnitude of Clinical Benefit Scale
NICE	National Institute for Health and Care Excellence
OECD	Organisation for Economic Co-operation and Development
PMDA	Pharmaceuticals and Medical Devices Agency (from Japan)
SIOPE	The European Society for Paediatric Oncology
WP	Work Package

Executive summary

Introduction

Horizon scanning systems (HSS) have been shown to be a useful tool to support policy makers and healthcare professionals in predicting the availability of new medicines and their main impacts. HSS help to gather, document and validate information on new medicines or indications before they are granted marketing authorisation or extension of authorisation for another indication. They usually ensure a complete and structured methodological approach of foresight activities.

The field of anticancer drugs has strongly evolved over the past years and the level of clinical development remains very large. Indeed, at the time of the analysis, about half of the ongoing clinical trials worldwide were in oncology. Moreover, in 2017, more than a third of requests for scientific advice to the European Medicine Agency (EMA) involved anti-neoplastic and immunomodulating agents. Innovative therapies in oncology, such as specific immunotherapies, are also associated with strong expenses and potential biomarkers conditioning their prescription.

This shows the importance of developing appropriate and robust methods to anticipate innovative therapies and their potential challenges in this therapeutic field.

The Work package 9 (WP9) of iPAAC, dedicated to innovative therapies in cancer, wanted to evaluate whether there was a need for more finesse in HSS to better anticipate innovative therapies in oncology. The WP9 main goals were to:

- identify the main existing HSS and collaborations in Europe and obtain a good understanding of their methodological characteristics;
- highlight and characterize methodological specificities needed for the identification and for the assessment of impact of innovative immunotherapies in cancer;
- identify the remaining challenges and perspectives to enable an efficient anticipation of innovative anticancer therapies and their potential clinical, economic and organizational impacts.

Method

A literature review was performed to identify existing horizon scanning systems in Europe as well as ongoing collaboration on this topic. It also helped the WP9 to identify relevant experts on the domain. Experts were invited for two distinct meetings on the topic to discuss potential specificities regarding the anticipation of anticancer drugs and remaining challenges.

A survey among organizations with a horizon scanning remit was conducted. Given their clinical, organizational and economic challenges, a strong focus was given in this survey to gene and cell therapies, pediatric indications as well as biomarkers. The survey was completed with a retrospective analysis. For 11 indications of immunotherapies, organizations were asked to indicate if it was correctly anticipated via their HSS and to provide eventual challenges encountered.

Results

Existing HSS in Europe and their main methodological features

Eleven main organizations in charge of a HSS with a focus on innovative drugs were identified in Europe, from which 9 replied to the iPAAC WP9 questionnaire.

Time frames of these 9 HSS ranged from 3 years to only a few months prior to marketing authorizations. HSS methodology varies a lot across organizations. For instance, only half of the organizations uses a structured database for the identification step, and half of them do not have a prioritization step. Public dissemination of HS outputs remains overall limited and is often in national language.

While most of the organizations included all innovative drugs in their scope, 2 were focusing only on oncology drugs.

Methodological specificities in HSS

Anticipation of innovative therapies in oncology

On the basis of the survey and feedbacks from experts during meetings, the anticipation of emerging anticancer drugs can require adaption of the HSS methodology. The 2 HSS focusing on oncology had developed specific methods to prioritize innovative anticancer drugs both strongly involving clinical experts. Moreover, specificities should also be considered depending on the type of cancer: available data can differ depending on the incidence, on the availability of anticancer drugs, and on the severity of cancer types.

Anticipation of gene and cell therapies

To enable a good anticipation of gene and cell therapies, it appeared valuable to screen early phases clinical trials and to collect additional data. For instance, for CAR-T cells, it was noted that the following information were interesting to collect to get a better idea of the impacts of these new drugs: target(s) of the CAR-T, generation, CAR-T construction method, nature autologous or allogenic with genomic editing method when applicable, use of a lymphodepletive chemotherapy prior to CAR-T administration, and number of injection planned. For these products, it appeared also important to obtain a good understanding of production steps and supply chain organization as early as possible in the development process to better anticipate potential related impacts on healthcare system, especially regarding organization of care.

Anticipation of biomarkers

Methodological specificities were also noted for the anticipation of biomarkers, especially the need to collect additional data. Information on biomarkers can be quite broad and varied, but the main focus in HSS seems to be given to companion test accompanying therapeutic indication depending on a biomarker expression. Overall, it appeared very important to identify as early as possible potential biomarker expression, on which indications could depend, to ensure the simultaneous implementation of the medicine and the diagnostic test.

Anticipation of pediatric indications

The way to address pediatric indications varies broadly across HSS. Whereas most of the HSS were treating pediatric indications with no specificities, two HSS did not include pediatric indications in the scope of their systems, one had developed a specific scoring method for prioritization, giving more weight to clinical development in pediatric population, and one estimated that the assessment of impact could be slightly different.

Remaining challenges and perspectives to enable an efficient anticipation of innovative therapies in oncology

Remaining difficulties for the anticipation of impacts linked to biomarkers and gene and cell therapies

According to the results of the retrospective analysis, most of the new indications with high clinical added value were easily identified and anticipated by organizations in charge of HSS. On the opposite, several difficulties were highlighted for the anticipation of impacts related to indications depending on a biomarker expression as well as for gene and cell therapies. For instance, biomarker expression threshold and centers authorized to provide gene and cell therapies or biomarker tests would be some of the hardest parameters to anticipate.

Identification and prioritization of innovative cancer therapies

Defining the time horizon in a HSS remains a difficult step: the identification of an upcoming clinically impacting medicine should be made as early as possible but should include sufficient robust clinical data to be exploited.

Having a structured database in the HSS process was seen as helpful, as it allowed the generation of ad hoc queries. Involving the expertise of practicing clinicians for prioritizing and assessing the innovative therapies bring also a strong support for predicting clinically impacting drugs.

Anticipation of clinical, organizational and economic impacts of innovative cancer therapies

Scales, such as the ESMO-MCBS or scoring methods, can be helpful methodological tools to assess the clinical impacts of innovative drugs. Nonetheless, it is important to implement tools that are adapted to the nature of clinical data usually available for innovative therapies such as non-comparative studies, immature data, and earlier studies for authorization. This is even more important for horizon scanning aiming to anticipate innovative therapies several years prior marketing authorization.

Pipeline meetings with pharmaceutical industries have been seen as a valuable resource to obtain details regarding the line of treatment and thus to better anticipate the place of the new treatment in therapeutic strategies. It could also help anticipating potential challenges related to production and supply. It remains however difficult to define how to involve pharmaceutical industries in the process of HSS without hindering the ethics of the implemented HSS and without limiting the publication of HSS output due notably to confidential data.

Promotion of HS outputs

Disseminating HSS results between all relevant actors in charge of the evaluation and of the financing of anticancer drugs is important to promote exchange and inter-institutional discussions around upcoming innovative therapies to facilitate their introduction on the territory. The timing and the content of HSS outputs should also be relevant to enable the implementation of early access programs when possible.

In order to reduce potential inequities in Europe regarding the anticipation of upcoming marketing authorization of innovative therapies, it would be very valuable to increase knowledge by sharing common tools, to make HSS outputs publicly available whenever possible and to continue to strengthen existing collaborations and initiatives on HSS.

Conclusion

Horizon scanning is a valuable resource for the proper introduction and diffusion of innovative drugs throughout the territory. Indeed, there was a consensus among organizations with a HS remit solicited by the WP9 that having a HS system in place enables a faster access to innovative therapies. HS systems provide an earlier and better basis for decisions making by health authorities and give the opportunity to act earlier in regard to recommendations and other introductory activities.

Although there is currently a minority of HSS specific to oncology, anticipating innovative drugs in oncology, and their potential related biomarkers, requires specific considerations, especially given the variety of drugs, the earliness of data supporting marketing authorization and the dynamics of this therapeutic area.

Pooling experiences and sharing challenges encountered in HSS at the European level will help enhancing the anticipation of new and emerging cancer therapies prior granting of their marketing authorizations as well as their related clinical, organizational and economic impacts.

Acknowledgment

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The WP9 also thanks the strong involvement from experts of the following organization for taking part to the WP9 meetings and/or for providing feedback to the questionnaire: the National Institute for Health Research Innovation Observatory of Newcastle University, UK; the Ludwig Boltzmann Institute for Health technology assessment from Austria; observers from the European Medicine Agency (EMA); the EUROSCAN network; the Clinical Research and Drug Assessment of the Local Health Authority of Verona, Italy; the National Institute for Health and Care Excellence (NICE); the International Horizon Scanning Initiative (IHSI); the Dutch healthcare institute, the AMGROS horizon scanning from Denmark, the Norwegian Institute of Public Health representing the EUnetHTA WP4, the Swedish Association of Local Authorities and Regions and National horizon scanning work group; the V.A. Trapeznikov Institute of Control Sciences of Russian Academy of Sciences; the Norwegian Medicines Agency horizon scanning team; the Portuguese Institute of Oncology of Coimbra Francisco Gentil.

1 Introduction

Cancer continues to present one of the key public health challenges in the European Union. Over the last 8 years, we have seen an intensification of the activities at the level of the European Union in order to tackle cancer from different aspects. Still, a number of important outstanding issues in cancer control remain unaddressed. The Innovative Partnership for Action Against Cancer (iPAAC), which has been selected for funding under the Third Health Programme 2014–2020, aims to build upon the outcomes of previous EPAAC and CANCON Joint Actions.

The general objective of the iPAAC Joint Action (JA) is to develop innovative approaches to advances in cancer control. The innovation that will be covered within the JA consists of further development of cancer prevention, comprehensive approaches to the use of genomics in cancer control, cancer information and registries, improvements and challenges in cancer care, mapping of innovative cancer treatments and governance of integrated cancer control, including a new analysis of National Cancer Control Plans. The key focus of the Joint Action is on implementation, reflected in the key deliverable: the *Roadmap on Implementation and Sustainability of Cancer Control Actions*, which will support Member States in implementation of iPAAC and CANCON recommendations.

As mentioned in the OCDE report published in November 2018, “Pharmaceutical Innovation and Access to Medicines”, there is a need to improve strategic intelligence activities, and to strengthen collaboration in this domain. This is why the WP9 has decided to focus its third task on the identification and prediction of impact of forthcoming innovative cancer treatment using horizon scanning systems (HSS).

Horizon scanning systems (HSS), also called early awareness and alert (EAA) systems appear to be useful tools to anticipate the arrival of impacting new therapies. HSS help to gather, document and validate information on new medicines or indications before they are granted marketing authorisation or extension of authorisation for another indication. They usually ensure a complete and structured methodological approach of foresight activities.

The number of anticancer drugs available has rapidly evolved over the past few years. Some innovative therapies have disrupted the landscape of therapies available. Due to the large number of ongoing clinical trials, many of them studying combinations of therapies, it will be a challenge to identify which therapies have a strong clinical added value and understand their impact on the health system.

Since most HSS generally have a global approach, not specific to oncology, the WP9 wanted to evaluate whether there was a need for more finesse on certain parameters, to better anticipate innovative therapies in the field of oncology. The WP9 main objectives were to:

1) identify the main existing HSS and collaborations in Europe and obtain a global understanding of their methodological features;
2) highlight and characterize methodological specificities within the existing systems for the identification and for the assessment of impact of innovative therapies in cancer;
3) identify the main difficulties and remaining challenges to enable an efficient anticipation of innovative therapies in oncology and of their potential related impacts.

This report provides a first part which presents some contextual facts including background information on HSS and key figures showing their importance in the oncology field.

Then, the main methodological steps that were followed to achieve the WP9 objectives are presented. Finally, the detailed results for each objective are described.

2 Contextual background information

2.1 Generalities on horizon scanning systems

2.1.1 Definition and goal

The main goal of a horizon scanning (HS) system is to anticipate the arrival on the market of new or emerging health technologies. HS systems usually follow a specific methodology with the following main steps: identification, filtration, prioritisation, assessment, dissemination and periodic update of information.

HS systems usually operate to answer to the questions of their relevant stakeholders such as policy makers, healthcare professionals or patients, and provide alert on potential impacts of these new or emerging health technologies in terms of:

- clinical aspects, such as their potential place in the therapeutic strategies;
- economic aspects, to anticipate potential financing issues related to the costs of the emerging health technology;
- organizational aspects, for instance impact on patient pathways, or organization of care.

In some cases, HS can also facilitate the implementation of early access programs for these new or emerging products.

Several terminologies can be used to designate these systems, such as:

- horizon scanning (HS) systems;
- early awareness and alert (EAA) systems;
- early warning systems.

2.1.2 HSS Methodology

The main steps of a HS process are described in Figure 1.

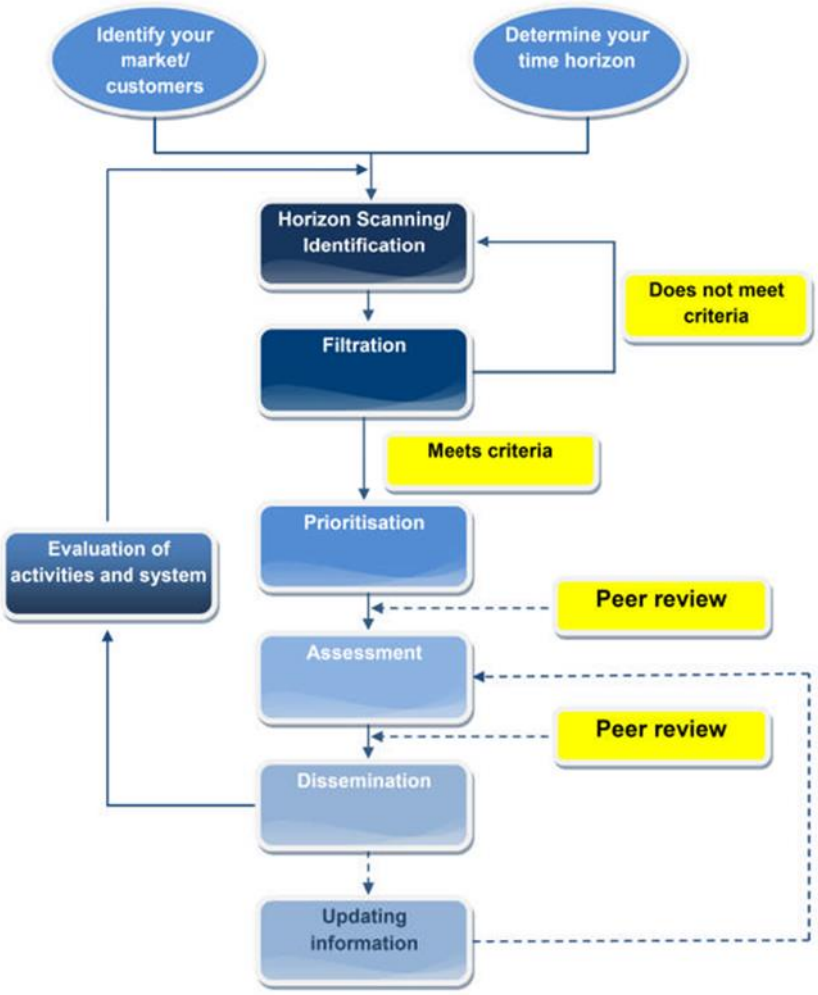

Figure 1: Horizon Scanning methodological steps

Source: EuroScan International Network, A toolkit for the identification and assessment of new and emerging health technologies, 2014, EuroScan International Network: Birmingham.

Additional information regarding horizon scanning methodology can be found through the EuroScan International Network website and toolkits (https://www.euroscan.org/index.php/en/), and in the KCE report.

In the case of pharmaceutical products, for the identification step, several sources of data can be used such as registries of ongoing clinical trials (e.g. clinicaltrial.gov; WHO international clinical trial registry platform). Some information available on the EMA website can also be a useful source of information, such as:

- designation of medicine for an orphan disease (https://www.ema.europa.eu/en/medicines/field_ema_web_categories%253Aname_field/Human/ema_group_types/ema_orphan?sort=field_ema_computed_date_field&order=desc);

- discussion for potential paediatric development: all new medicines need to be discussed and outcomes of these discussions are made public and can give an idea about the types of products and targeted diseases (https://www.ema.europa.eu/en/medicines/field_ema_web_categories%253Aname_field/Human/ema_group_types/ema_pip?sort=field_ema_computed_date_field&order=desc);
- list of medicines under evaluation for a centralised marketing authorisation: information published at the start of the procedure (https://www.ema.europa.eu/en/medicines/medicines-under-evaluation);
- CHMP meeting minutes (https://www.ema.europa.eu/en/committees/chmp/chmp-agendas-minutes-highlights).

2.1.3 Main steps to define before the implementation of an Horizon Scanning System

1) Target

The most common users of horizon scanning outputs are national or regional agencies performing health technology assessment (HTA). Indeed, horizon scanning systems are often seen as a basis to perform the identification and/or an early assessment of the emerging technology.

However, various stakeholders can be interested by such systems such as payers, especially to anticipate potential costs, policymakers, medicines agencies to anticipate upcoming workload and the need for new expertise and healthcare professionals to anticipate impact on clinical practices. It can also help organizations providing clinical practice guidelines to better predict when there is a need to revise current versions.

Finally, a HS process can also provide some relevant information for patients and their relatives as they could be interested to know what will be the medicines of tomorrow. Associations of patients can also take interest into HS results to initiate collective actions.

2) Scope

Some HS systems can be very broad and include all types of emerging health technologies. However, the scope can sometimes be narrowed to anticipate more specifically one type of emerging health technologies such as medicines or medical devices. Some HS systems are even more focused on one specific therapeutic area only, such as oncology.

When the scope of a HS system is restricted to drugs, the goal is to anticipate incoming new therapies and their main impacts, before they obtain the marketing authorization.

3) Expected outputs

Organizations in charge of a HS system need to define what type of outputs and deliverables they expect to produce through their process.

Different types of outputs are worth considering.

- Some HS systems chose to maintain a database up to date which could include very broad and various data such as name of the product, indication, clinical trial results, health authority priority review status, and so on.
- The list of prioritized drugs, possibly including scoring.
- HS report, also called alert report, technology briefing, or early assessment report, can be issued based on the work conducted by the HS team, depending on the assessment extend. The level of information included in these briefing reports depends mainly on the target of the report. For innovative therapies, some minimum information such as the therapeutic class and the indication should be specified. Expected clinical benefits, adverse events and costs are interesting to be collected. Some organizations provide reports with in-depth analysis of the impact (clinical, organizational, and/or economic).

The content of the output should of course be adapted according to the target of the information.

4) Time frame

Each organization in charge of a HS system has to define how long prior the marketing authorization they want to know about upcoming innovative therapies. This is called the time frame or time horizon and it should be defined upstream of the implementation of the system.

5) Budget

It is important to anticipate costs associated with the implementation of a HS system such as the functioning of the database, experts reviewing and assessing data.

6) Governance

Organizations in charge of HS systems should define who will be in charge of the system (e.g. ministry of health, public body, association) and who is responsible for the possible maintenance of database, website. They should also decide whether some outputs are made publically available or if results are restricted to specific stakeholders.

Some organizations use external providers for the implementation of HS services. This should also be anticipated with market tender.

2.2 Key figures associated with innovative treatments in the oncology field

The WP9 analyzed ongoing clinical trials, requests for scientific advice to medicine agencies, anticancer drug entries in accelerated market access programs and new marketing authorizations, including extensions of indications, in order to get a better idea of the proportion of innovative drugs in the oncology field and to confirm the need for readiness in this therapeutic area.

2.2.1 Oncology in the clinical development

On the 7th of December 2018, about 44% of the research studies entered in clinicaltrial.gov involved the oncology therapeutic area. Indeed, there were 127 146 studies entered on clinicaltrial.gov in the field of oncology (gathering terms: cancer, neoplasm, tumor, malignancy, oncology, neoplasia, neoplastic syndrome, neoplastic disease) out of the 291 628 studies in total in the database.

This number seems to continue to grow. Indeed, 10 months later, on the 7th of October 2019, 154 666 out of 318 388 were in the oncology field, so approximately 48,6% of studies.

As per the LEEM ninth survey on the Attractiveness of France for International Clinical Research, 45% of industrial clinical trials started in France between the 1st of January 2016 and the 31st of December 2017, involved cancer.

As per the IQVIA report "Global Oncology Trends 2018, innovation, expansion and disruption", more than 700 cancer drugs were in late-stage development in 2017. Over one-third of trials are using biomarkers to stratify patients, pointing to even more personalized (and effective) cancer treatments in the future.

2.2.2 Oncology in scientific advice requests

The therapeutic area for which there was the most scientific advice requests in 2017 to the European Medicine Agency (EMA) was the anti-neoplastic and immunomodulating agents (229 requests out of 630: 36%).

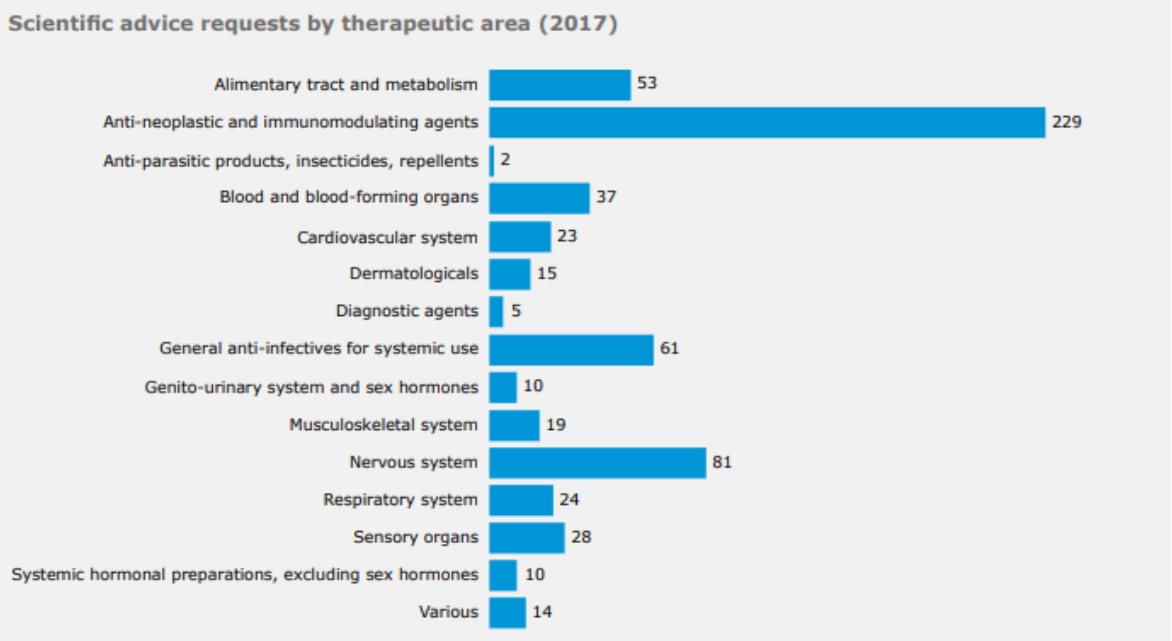

Figure 2: Distribution of scientific advice requests from 2017 to EMA by therapeutic area

Source: European Medicines Agency. Annual report 2017

2.2.3 Oncology in early access programs

A total of 34 medicines entered the EMA PRIME scheme between its launch in March 2016 and December 2017. The most represented therapeutic area was cancer, with a total of 12 medicines achieving the PRIME status (35%).

As a reminder, the EMA initiative PRIority MEdicines (PRIME) scheme was launched in March 2016 to provide early and enhanced support to medicines that can potentially address patients' unmet medical needs. To be accepted for PRIME, a medicine has to show its potential to benefit patients with unmet medical needs based on early clinical data. Between its launch in 2016 and December 2017, EMA received and reviewed a total of 154 applications for PRIME.

Among the 12 novel drugs approved in the oncology field in 2017 in the USA, 11 used at least one expedited pathway like the priority review (11), breakthrough therapy (9), accelerated approval (5 out of 6 in total), and fast track (6).

2.2.4 Drugs arriving on the market in the oncology field

In 2017, EMA recommended 92 medicines for marketing authorization. Of these, 35 contained a new active substance, i.e. one which had never previously been authorized in the EU, and 11 out of these 35 medicines were approved in the oncology field (31%).

In the United States in 2017, CDER approved 46 novel drugs, with 12 in the oncology area (26%). Of note, CAR-T cells were also approved in 2017, by the CBER. They were the only two drugs approved in the oncology field by the CBER.

As per the IQVIA report on Global trends in Oncology 2018, over the past five years, there were 61 new active substances approved for a total of 76 indications, impacting the treatment of 23 different cancer types.

It is interesting to see the evolution of indications for the two anti-PD-L1 nivolumab and pembrolizumab which have both received respectively a total of 12 and 10 approvals from the FDA for several new indications or extension of indications between September 2014 and February 2018. Anti-PD-1 and anti-PD-L1 are now being used across almost all tumor types.

2.2.5 Healthcare expenses related to oncology

Global spending on cancer therapies and supportive care drugs exceeded $133 billion in 2018, according to the IQVIA report on Global trends in Oncology 2018.

As per the OECD report on Pharmaceutical Innovation and Access to Medicines, "Despite a slowdown in growth in the 2000s, pharmaceutical spending has nevertheless increased sharply in some therapeutic areas, such as oncology and certain rare diseases where many new medicines target small population groups and command high prices. While these may well address unmet needs, they often have prices that may not be justified by the health benefits they confer".

In conclusion to this contextual background part, it is important to stress that innovative therapies in oncology such as specific immunotherapies are associated with:

- **a large and increasing clinical development with more and more association;**
- **a strong potential impact on therapeutic strategies with development in clinical situations where there is a medical need;**
- **potential biomarkers conditioning their prescription;**
- **high prices and considerable expenses.**

That is why, it is of major importance to anticipate the arrival on the market of these drugs with robustness.

3 Methodology

The discussion on the detailed methodology started with the WP9 partners on 02-03 July 2018 during the WP9 kick-off meeting organized by the French National Cancer Institute (INCa) in Paris. Knowing that there are currently many ongoing initiatives on HS, the WP9 wanted to propose a work plan avoiding any duplication of work, but rather to create synergies and to strengthen collaboration, keeping in mind that each country/organization might have different expectations from a HS system.

Four methodological steps were followed to answer the WP9 objectives:

1) a literature review of existing horizon scanning systems and related initiatives;
2) the organisation of 2 dedicated meetings to collect experts, partners and stakeholders feedback;
3) a questionnaire among organizations in charge of a HS program;
4) a retrospective analysis for the anticipation of 11 indications of innovative immunotherapies.

Each of these 4 steps enabled to cross-answered the 3 main WP9 task 3 objectives.

3.1 Literature review of existing horizon scanning systems and related initiatives

A literature review was performed in order to identify existing horizon scanning systems in Europe as well as existing collaborations on this topic. It also helped the WP9 to identify relevant experts on the domain.

Several searches were conducted on PubMed, on Google and on websites of health, medicines and HTA agencies. Several key words were used including: “horizon scanning systems”, “early awareness systems”, “early alert systems”, and “anticipation of innovative therapies”.

The Belgian Health Care Knowledge Centre (KCE) report on HSS was a useful support for information as they already benchmarked existing systems back in 2017 (https://kce.fgov.be/en/horizon-scanning-for-pharmaceuticals-proposal-for-the-beneluxa-collaboration).

3.2 Organisation of 2 dedicated meetings to collect stakeholders, partners and experts feedback

Two dedicated meetings were organized with a focus on the iPAAC WP9 task 3.

The first meeting occurred on the 6th of March 2019 in Brussels with the WP9 associated and collaborative partners as well as several experts. The goal of the meeting was to give the opportunity to several experts to present their own HSS. We also aimed at presenting existing European collaboration on the topic in order to strengthen the link within the community and make sure to avoid duplication of work. It was also the opportunity to obtain feedback from HTA and medicines agencies (NICE, EMA) regarding HSS. Finally, the questionnaire was presented and reviewed with WP9 partners and experts prior dissemination (see paragraph 3). The minutes of this first meeting are available in appendix 7.1.

A second meeting was organized on the 18th of November 2019 in Boulogne-Billancourt. It aimed at:

- presenting the results of the questionnaire (see part 4 “Results” for details); and make sure the results obtained were properly interpreted;
- presenting and discussing innovative approaches in horizon scanning systems and identifying potential One-pagers;
- validating the content of the task 3 deliverable as well and review remaining challenges.

The minutes of this second meeting are available on appendix 7.2.

Feedback from relevant experts, stakeholders and partners was additionally collected throughout the conduct of the work (mainly by email).

3.3 Questionnaire among organizations in charge of a HS program

3.3.1.1 Construction and content

The questionnaire was developed in February 2019 by the INCa team and the first version was collectively reviewed and completed at the first meeting with experts.

The final version of the questionnaire is available in appendix 7.3: “Questions addressed to organizations in charge of a horizon scanning system”.

The questionnaire was structured in 3 parts to answer the different WP9 objectives.

1) General questions on HSS and their methodology

Questions related to the scope, the time frame, the methodology (use of a database, prioritization step) and to the production and dissemination of outputs, were included to obtain an overall understanding of the methodological aspects of existing HSS.

2) Questions regarding specificities in oncology

Several questions were integrated to identify potential methodological specificities for:

- oncology medicines;
- gene and cell therapies;
- biomarkers.

Following the first meeting with experts and partners, a question was also added to capture potential methodological specificities for paediatric indications following recommendations from the WP9 collaborating partner from the European Society for Paediatric Oncology (SIOPE).

3) Questions related to the retrospective analysis

Details are provided on section 3.4 of this document.

3.3.1.2 Target and dissemination

The questionnaire was addressed to persons involved in the implementation of a HSS and to organizations with a HSS remit.

For the dissemination of the survey, experts were identified through existing network and online. The WP9 sent the questionnaire directly to experts identified.

The European Hospital and Healthcare Federation (HOPE) and the EuroScan International Network also disseminated the questionnaire among their members.

3.4 Retrospective analysis for the anticipation of 11 indications of innovative immunotherapies

The retrospective analysis was conducted in order to identify strengths of existing HSS as well as difficulties encountered in the oncology field. For this purpose, 11 indications of innovative immunotherapies were selected. For each of them, the goal was to assess if the indications were properly identified by the HSS prior marketing authorizations and if their main impacts were correctly anticipated. It was also the opportunity to highlight potential challenges encountered for the anticipation of these emerging therapies and their clinical, organizational and economic impacts.

This retrospective analysis was conducted in two steps:

- the analysis of the questionnaire replies;
- a review of published HSS reports for these indications.

3.4.1 Indications reviewed

The WP9 selected a panel of specific indications of innovative immunotherapies which had been recently approved by the EMA. Considering the large number of existing indications, the WP9 decided to select 11 indications which could reflect most types of innovative and clinically impacting indications including: indications depending on a biomarker expression, gene and cell therapies, and indications of checkpoint inhibitors with high clinical added value. To assess the clinical added value, the WP9 based the selection on the scores attributed by the French HTA agency: Haute Autorité de santé (HAS).

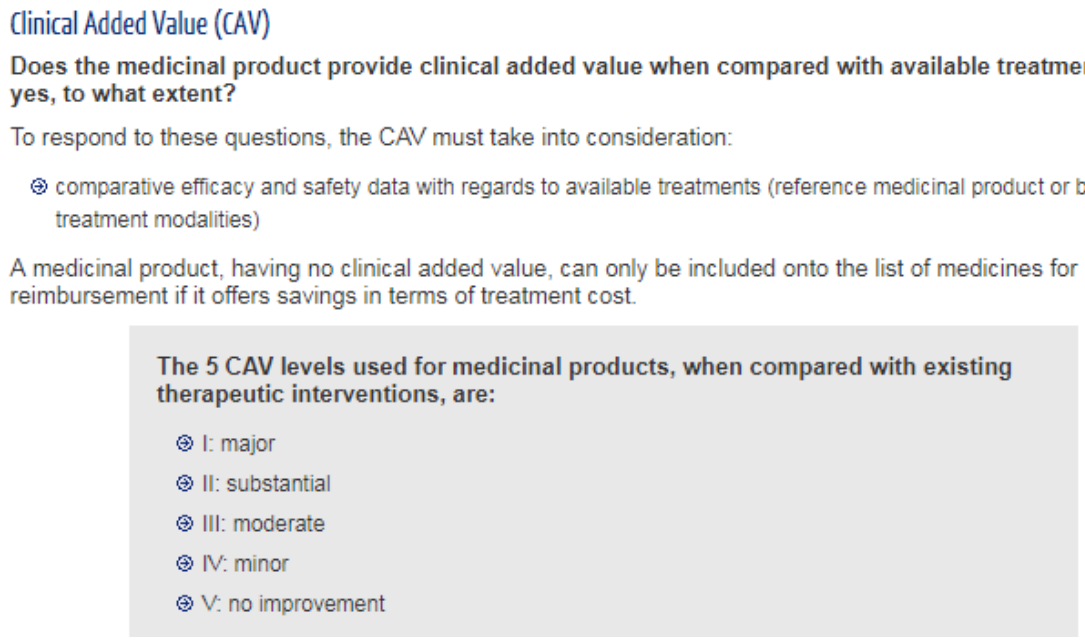

Figure 3: Clinical Added Value levels from the French HTA agency (Haute Autorité de santé)

Source: HAS. More info on the HAS website: https://www.has-sante.fr/portail/jcms/c_2035651/en/methods-and-criteria-for-assessing-medicines#toc_1_2

The following 11 indications were selected:

- 4 indications depending on the expression of a specific biomarker:
  - Pembrolizumab (Keytruda) as monotherapy for the treatment of locally advanced or metastatic NSCLC in adults whose tumours express PD-L1 with a ≥1% TPS and who have received at least one prior chemotherapy regimen. (Patients with EGFR or ALK positive tumour mutations should also have received targeted therapy before receiving KEYTRUDA).
  - Pembrolizumab (Keytruda) as monotherapy for the first-line treatment of metastatic non-small cell lung carcinoma (NSCLC) in adults whose tumours express PD-L1 with a ≥50% tumour proportion score (TPS) with no EGFR or ALK positive tumour mutations.
  - Durvalumab (Imfinzi) as monotherapy for the treatment of locally advanced, unresectable non-small cell lung cancer (NSCLC) in adults whose tumours express PD-L1 on ≥ 1% of tumour cells and whose disease has not progressed following platinum-based chemoradiation therapy.
  - Atezolizumab (Tecentriq) as monotherapy for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma (UC): - after prior platinum-containing chemotherapy, or –who are considered cisplatin ineligible, and whose tumours have a PD-L1 expression ≥ 5%.

- The 3 indications of CAR-T cells approved in 2018:
    - Tisagenlecleucel (Kymriah) indicated for paediatric and young adult patients up to 25 years of age with B‑cell acute lymphoblastic leukaemia (ALL) that is refractory, in relapse post‑transplant or in second or later relapse.
    - Tisagenlecleucel (Kymriah) indicated for adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy.
    - Axicabtagene ciloleucel (Yescarta) indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and primary mediastinal large B-cell lymphoma (PMBCL), after two or more lines of systemic therapy.

- 4 indications with a level of Clinical Added Value (CAV) ≥ III
    - Nivolumab (OPDIVO) as monotherapy for the treatment of advanced (unresectable or metastatic) melanoma in adults.
    - Nivolumab (OPDIVO) as monotherapy for the adjuvant treatment of adults with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection.
    - Nivolumab (OPDIVO) as monotherapy for the treatment of advanced renal cell carcinoma after prior therapy in adults.
    - Nivolumab (OPDIVO) as monotherapy for locally advanced or metastatic squamous non-small cell lung cancer (NSCLC) after prior chemotherapy in adults.

Of note, the indication of pembrolizumab as monotherapy for the first-line treatment of metastatic NSCLC in adults whose tumours express PD-L1 with a ≥50% tumour proportion score had also been assessed as CAV of III by the French HAS.

3.4.2 Analysis of the 11 indications through the questionnaire results

The third part of the questionnaire included questions to perform the retrospective analysis. For each of the 11 indications, the organizations in charge of a HSS were asked to answer the following questions.

1) Was your system enabling the identification of this indication prior marketing authorization?
2) Reason for no identification via Horizon Scanning if applicable (e.g. methodological gap, not included in the scope, …).
3) Was an assessment report publicly published for this indication?
4) Rate the assessment report provided by your organization regarding the estimation of impact of the new indication (rate your evaluation by giving a grade between 1 and 10, 10 being the best: very good anticipation of impact of this new indication, and 1

the lower: many challenges did not enabled us to correctly anticipate the impact of this indication).

5) Indicate eventual challenges encountered for the assessment of impact of this new indication.

For indications depending on the expression of a specific biomarker, an additional question was added in order to know if the associated companion test was also anticipated with the HSS. To be noted, the companion (diagnostic) test definition considered was the one included in the glossary of the HAS methodological guide on this topic: “diagnostic test permitting the selection only of patients in whom the treatment is likely to provide a benefit from among those diagnosed with a given illness, according to their status for a predictive marker identified by this test” (https://www.has-sante.fr/jcms/c_1735034/en/companion-diagnostic-test-associated-with-a-targeted-therapy-definitions-and-assessment-method).

3.4.3 Analysis of the 11 indications through a review of HSS assessment reports published

A review of publications from HS organizations was performed for the 11 indications selected. The websites of the each HS system were consulted in order to identify HS reports published for each indication.

HS reports with content available in English were reviewed, especially regarding the information on gene and cell therapies and biomarkers, in order to assess whether challenges associated with these indications had been foreseen and if some difficulties had been highlighted.

4 Results

4.1 Existing horizon scanning systems in Europe and collaborations

4.1.1 Individual horizon scanning systems in Europe and their main methodological features

4.1.1.1 Organizations in charge

Various types of organization in charge of HSS were identified such as independent research center, local health authority, healthcare institute, oncology care institute and national cancer institute.

Several medical centers or hospitals also seem to have their own HSS. However, it was hard to get a clear understanding of the methodology in place for these systems; and alerts are rarely written with the purpose of being widely disseminated and usually remain internal.

More and more organizations also developed foresight activities, not always as structured as a HS process, but which provide some good elements to anticipate the arrival of new and emerging health technologies.

The main European horizon scanning systems already implemented and with a focus on innovative drugs in their scope are presented in the Table 1.

Table 1: European implemented Horizon Scanning systems dedicated to innovative drugs

Country	Organisation	Additional information
Austria	Ludwig Boltzmann Institute*	https://hta.lbg.ac.at/page/horizon-scanning-in-der-onkologie/en
Denmark	Amgros	https://www.amgros.dk/en/
England	National Institute for Health Research Innovation Observatory	http://www.io.nihr.ac.uk/
France	French National Cancer Institute	https://www.e-cancer.fr/Professionnels-de-sante/Medicaments
Italy	Italian horizon scanning project	https://hal.archives-ouvertes.fr/hal-00534965/document
Netherlands	National Healthcare Institute	https://www.horizonscangeneesmiddelen.nl/geneesmiddelen
Norway	horizon scanning at the Norwegian Medicines Agency	https://legemiddelverket.no/english/public-funding-and-pricing/horizon-scanning
Portugal	Portugese Institute of Oncology of Coimbra Francisco Gentil	https://ipocoimbra.com/
Scotland	Scottish Medicines Consortium	https://www.scottishmedicines.org.uk/about-us/horizon-scanning/
Sweden	New Therapy Council Swedish Association of Local Authorities and Regions and National horizon scanning work group	https://www.janusinfo.se/nationelltordnatinforande/managedintroductionthisishowitworks/inenglish/horizonscanning.5.4771ab7716298ed82ba97406.html
Wales	New Medicines group from the “All Wales Medicines Strategy Group”	http://www.awmsg.org/nmg_about_us.html

** Since January 2020, the activities of the Ludwig Boltzmann Institute have slightly changed and are now part of the Austrian Institute for Health Technology Assessment (AIHTA).*

Replies to the WP9 questionnaire were collected from 9 out of the 11 organizations identified in Table 1, from the following countries: Austria, Italy, Netherlands, England, Portugal, Sweden, Denmark, Norway and France.

Another reply from Russia was received mentioning that there is no official procedure for horizon scanning in Russia, but horizon scanning is being included in research programs linked to access to medicines or/and interventions.

4.1.1.2 Scope

The names and scopes of the HSS for which a reply to the questionnaire was provided are presented in Table 3. While most of the organizations included all kind of innovative drugs in the scope of their HSS, 2 organizations, those in Austria and in France, were focusing specifically on oncology drugs.

Table 2: Overview of organizations participating to the WP9 survey and scope of their HSS

Country	Organisation	Scope
Austria	Ludwig Boltzmann Institute	Oncology, focus on drugs
Denmark	Amgros	All therapeutic areas, focus on drugs
England	National Institute for Health Research Innovation Observatory (NIHRIO) Newcastle University	Innovations and new technologies (not limited to drugs, with the exception of prophylactic/preventive vaccines, dietary supplements and generic drugs)
France	French National Cancer Institute (INCa)	Oncology, focus on drugs
Italy	Italian horizon scanning project	All therapeutic areas, focus on drugs
Netherlands	National Healthcare Institute	All therapeutic areas, focus on drugs (less information published for biosimilars and generic drugs)
Norway	Horizon Scanning at the Norwegian Medicines Agency	All therapeutic areas, focus on drugs
Portugal	Portugese Institute of Oncology of Coimbra Francisco Gentil	Oncology
Sweden	New Therapy Council Swedish Association of Local Authorities and Regions and National horizon scanning work group	All therapeutic areas, focus on drugs

4.1.1.3 Time Frames

Time frames to identify new medicines and indications ranged from 3 years prior EU MA (Italy, England) to only a few months prior EU MA (Austria). The figure below presents how long prior granting of marketing authorization, the HSS identify new and emerging medicines/indications.

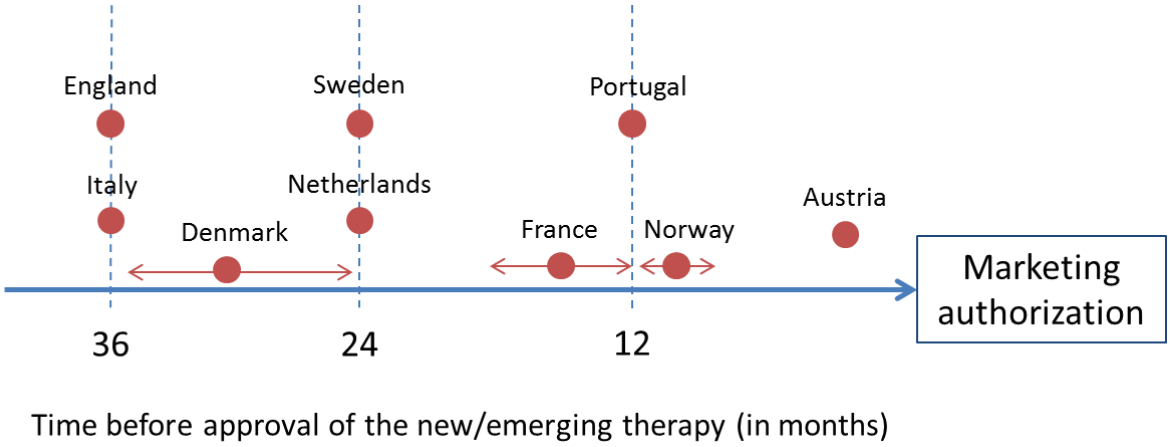

Figure 4: Repartition of HSS time frames across Europe

Source: INCa

4.1.1.4 Identification

5 HSS out of the 9 for which replies were collected mentioned that they use a structured database to identify drugs in development. In addition, for the NIHRIO HSS in England, it was specified that they do not currently have a completely automated database, however they are developing natural language processing/text mining tools which could be used in the future.

4.1.1.5 Filtration and prioritization

First of all, it is important to note that not all organization have a prioritization step. For instance, the Dutch, the Danish and the Norwegian HSS do not prioritize between medicines.

Italy, England, Portugal and Sweden do not use a scoring method for prioritization.

4.1.1.6 Assessment and dissemination of HSS outputs

Some organizations in charge of HSS assess the impacts of innovative medicines themselves; other provide summary data or briefing reports to other organizations in charge of the assessment.

Examples of organizations working jointly with other entities were provided in questionnaire replies. In the UK, the NIHR IO works very closely with the National Institute for Health and Care Excellence (NICE) in England who is charge of performing the assessment. In Denmark, reports are published by the Danish Medicine Council. In the Netherlands, assessments are only made after registration and are not part of the HS process. Dutch HS outputs are however

used as a starting point for the assessment including information available at the time, brief estimate of the patient volume and the expected value for Dutch Healthcare.

The publication of HS reports is not systematic: some of them remain confidential. Most of them are published in national language, except for Austria where reports are all available in English.

Some countries also publicly publish the list of prioritized drugs such as Austria and Sweden. France is also planning on publicly publish their list of prioritized drugs.

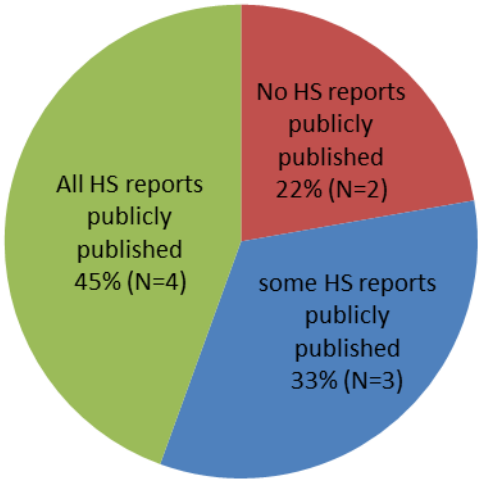

Figure 5: Repartition of organizations depending on HSS output publications (questionnaire results)

Table 3 presents a brief description of information available on the website of HSS publishing detailed results by molecules or indications.

Table 3: Overview of organizations publishing outputs from horizon scanning and content description

Organizations publishing information from HSS	Country and language	Brief description of information available on their website
National Institute for Health Research Innovation Observatory from Newcastle University	UK - English	- Launched in 2017 but includes on their website reports previously prepared by Birmingham university. - HS briefing reports contain information on the estimated impact on therapeutic strategies and estimated costs of innovative therapies. - Some HS briefing reports contain information on potential companion test provided (but not systematically).

NHS Specialist Pharmacy services	UK - English	- Presents one page per molecule (including several indications if applicable). - The website is regularly updated. - Audience targeted: mainly patients and HCP. - It seems that there are no reports published prior February 2016: might explain the delay of identification for drugs approved prior this date. - From the information available, it seems to be hard to anticipate which biomarker test will be necessary for the prescription of these drugs in the routine practice. - Not much information on the impact that the drug might have on organization of care. - Almost no information about estimated costs. - Provide links to NICE evaluation.
Ludwig Boltzmann Institute	Austria - English	- Publish PDF reports in English. - Reports includes: drug description, indication, current regulatory status, burden of disease, current treatment, description of the evidence available (efficacy and safety), estimated costs. - Publish lists of prioritized medicines in English. - Methodological tools available on the website (e.g.: support for budget-impact calculation).
National Healthcare Institute	Netherlands - Dutch	- Information not published in English. - Reports can be organized and filtered by therapeutic area, molecules and divided per indication, if several, by planned registration data. - Page updated every 6 months.
MedNytt from the Norwegian Medicines Agency	Norway - Norwegian	- Information not published in English. - PDF reports in Norwegian.
Amgros Horizon Scanning	Denmark – Danish and English	- Overviews in Danish. - Reports in Danish. - Pipeline meetings in Danish. - Newsletter: sign up and recive the latest news form HS in Danish. - Find your way through EMA in Danish. - Overviews in English. - Pipeline meetings in English. - Newsletter: sign up and recive the latest news form HS in English. - Find your way through EMA in English.

4.1.1.7 Link between HSS and access to innovative therapies

All questionnaire responders agree to say that having a HS system in place enables a faster access to innovative therapies.

It was highlighted that HS gives the opportunity to act earlier in regard to recommendations and other miscellaneous introductory activities.

HS collect information on coming drugs and/or new indications before launch. This provides an earlier and better basis for making decisions by authorities.

4.1.2 Collaborations on horizon scanning in Europe and beyond

Several initiatives on HS are ongoing in Europe and beyond.

EuroScan International Network is a non-profit scientific association shaped as a global collaborative network of public agencies, scientific organisations, and individuals. EuroScan aims to collect and share information on emerging, new, and obsolete health technologies to support decision-making on their adoption, appropriate use, and need of re-assessment. EuoScan aims to be the main global forum for sharing and developing methods for HS. The network acquired legal status in 2017, but was established already twenty years before as a working group of public agencies that contributed widely to develop and share methods and information. EuroScan provides to its members a forum to share skills and experiences together with tools and services (e.g., online exchange platform, database of technologies) and has scientific collaborations with external partners to improve and develop methodological approaches. Moreover, the network in engaged in advising non-profit organisations who wish to consider the establishment of HS activities (https://www.euroscan-network.global/index.php/en/about).

Then, the EUnetHTA joint action has one work package dedicated to HSS. They wrote a draft report which was open for public review in the summer 2018: “Horizon Scanning, Topic Identification, Selection and Prioritization for European cooperation on HTA’ draft recommendations“. Pilot studies for topic identification, selection and prioritisation have been conducted. EUnetHTA published at the beginning of 2020 a list of prioritized topics for joint assessment (https://eunethta.eu/assessments/prioritisation-list/).

The BeNeLuxA initiative gathered forces from several countries to develop a common HSS, called the “International Horizon Scanning Initiative“ (IHSI). An open market consultation took place at the end of 2018 to inform companies and organisations regarding the upcoming public procurement procedure for setting up this common HSS (https://ihsi-health.org/). This HSS is not yet in place.

Countries involved in the Valletta declaration (Croatia, Cyprus, Greece, Ireland, Italy, Malta, Portugal, Romania, Slovenia and Spain) have agreed to integrate HS of innovative therapies as a focus of their activities (Presentation from Paola Testori Coggi, Chair of the Valletta Technical Committee, from 29-30 November 2018 in Lisbon; https://www.infarmed.pt/documents/15786/2835945/Paola_Testori_Coggi.pdf/2388762b-7506-4a78-9533-7422ea480c55).

The International Coalition of Medicines Regulatory Authorities (ICMRA) has an initiative on innovation. According to the ICMRA note on Strategic Priority on Innovation, written in October 2017, 3 main work streams were selected:

- Horizon scanning: methodologies and best practice (led by PMDA – Japan).
- Horizon scanning outcomes: products; technologies; regulatory science approaches and expertise requirements (led by EMA) with 3 case studies:
    - Genome editing (off-target, lifetime effects, immunogenicity, ethics).

    - Additive manufacturing (e.g.: software validation, Application Programming Interface).
    - Artificial Intelligence (infrastructure, algorithms, big data).
- Novel approaches to licensing, identification of barriers and methods to address these (Health Canada).

The EU-Innovation Network, gathering the European Medicine Agency (EMA) and the Heads of Medicines Agencies (HMA), also work on anticipating emerging new trends and technologies. (https://www.hma.eu/495.html)

Pharmaceutical industries are also actively involved in horizon scanning activities through existing networks of industries such as *Les Entreprises du Médicament* (LEEM) in France and the European Federation of pharmaceutical industries and associations (EFPIA) in Europe. (https://www.leem.org/europe-et-international)

Since 2004, the Joint Research Center of the European Commission also organises future-oriented technology analysis conferences with the aim to develop communities of foresight, forecasting and technology assessment. Here experts interact and help in guiding strategy, policy and decision-making to anticipate and shape future developments (https://ec.europa.eu/jrc/en/research/crosscutting-activities/foresight). There is also a European foresight platform supported by the European Commission (http://www.foresight-platform.eu/).

4.2 Methodological specificities in horizon scanning systems

4.2.1 Specificities for oncology medicines

Two European horizon scanning systems are focusing only on innovative drugs in the field of oncology: the HSS from INCa in France and from the Ludwig Boltzmann institute in Austria. The methodology developed for these 2 HSS was thus adapted specifically for this therapeutic area. For instance, in Austria, phase II trials are included in addition to phase III trials for orphan drugs. In France, the HSS includes in its database phase IB to III trials.

Specific prioritization methods have been developed for the 2 HSS focusing on oncology drugs:

- *the Austrian system of the Ludwig Boltzmann institute*

For the prioritization step, the Ludwig Boltzmann institute in Austria implemented an evaluation performed by external experts via 5 relevant criteria for a maximum of 10 relevant indications quarterly. The five criteria assessed are:

- existence of an alternative therapy (treatment available or new therapy);
- place of the new therapy (add-on or replacement or new therapy);
- clinical impact/health benefit (minor/major);
- economic impact (minor/major);
- potential for inappropriate use (minor/major).

According to these 5 parameters, experts should then choose the category: highly relevant, relevant or not relevant. The assessment is performed if the category highly relevant is chosen; drugs are monitored if relevant; and drugs are dropped out if not relevant.

- the French horizon scanning of the French National Cancer Institute (INCa)

INCa has developed a prioritization approach by using a scoring method of innovative therapies in order to help prioritizing clinically impacting drugs. First, a score between 0 and 100 is attributed to each filtered drug, by the service provider, on the 6 following families:

- added therapeutic value;
- entering a specific early access program in France;
- regulatory innovation;
- pediatric population;
- incurable disease;
- large population.

Then, French stakeholders (e.g. cancer societies or organ specific societies) attribute a second score between 0 and 100 to each filtered drug, according to their view on the potential clinical impact.

The final score is the mean of these 2 scores. Based on this score the list of prioritized medicines is composed.

From the questionnaire results, the HSS from the Portuguese Institute of Oncology of Coimbra Francisco Gentil and from AMGROS in Denmark notably mentioned that they could include clinical trials in earlier phases and collect additional data. Moreover, in Portugal, they also use a different method for assessment of impact for oncology medicines.

Nonetheless, it was highlighted at the second iPAAC WP9 task 3 meeting, that specificities should also be considered across cancer types. Available data can indeed differ depending on the incidence, on available anticancer drugs, and on the severity of cancer types. Comparative data are usually more common in large spread cancers compared to rarer cancers. For instance, it is easier to obtain comparative data in large spread cancer such as prostate and breast cancer, whereas in hematologic cancer for instance, it might be harder.

4.2.2 Specificities for gene and cell therapies

In Denmark, for gene and cell therapies, AMGROS HSS includes earlier phase clinical trials.

France has implemented the collection of additional data for gene and cell therapies, and more particularly for CAR-T cells. Indeed, for CAR-T cells, the following information is collected and reviewed:

- target(s) of the CAR-T;
- generation;
- CAR-T construction method;
- nature autologous or allogenic with genomic editing method when applicable;
- use of a lymphodepletive chemotherapy prior CAR-T administration;
- number of injections planned.

Furthermore, it was highlighted at the second iPAAC WP9 task 3 meeting that it is of main interest to anticipate the site of production for these products in order to better anticipate their arrival on the market. It appears indeed important to obtain a good understanding of production steps and supply chain organization as early as possible in the development process to better anticipate potential related impacts on healthcare system, especially regarding organization of

care. The production of CAR-T cells involves a complex therapeutic course and patients' cells have to be transported in some cases across borders. Thus, production time for CAR-T cells can be significant, ranging from 14 to 51 days according to the ELIANA trial (pivotal study supporting the approval of Kymriah® for its indication in acute lymphoblastic leukemia). Considering that patients treated with CAR-T cells are at a very advance stage of the disease, the length of production and production sites are important parameters to anticipate, because they can have significant consequences on the availability of treatments.

4.2.3 Specificities for biomarkers

4.2.3.1 Type of information identified and collected regarding biomarkers in HSS

Most of the existing European HSS aim to identify potential predictive biomarkers linked with new therapies, and they usually include related information in HSS reports when available and relevant.

Only the Dutch HSS does not collect information on biomarkers, mainly due to the fact that another institution, the Hartwig Medical Foundation, is responsible for generating an overview on this aspect.

Information collected on biomarkers can be quite broad and varied, but the main focus seems to be given to companion test accompanying therapeutic indication depending on a biomarker expression.

In Austria, they are able to "detect those biomarkers that are related to a therapeutic indication and potential tests that are used to identify the specific patient population. Since oncology drugs are often approved earlier in the US and the FDA also approves biomarker tests we are able to identify it."

In Italy, therapeutic indication depending on a biomarker expression and contemporary development of a companion test are specified.

In England, all the following information can be collected: cells, genes (DNA), gene modification (methylation), gene products- mRNA transcripts (RNA), proteins, enzymes, peptides, autoantibodies, steroids, and hormones.

In Sweden, information collected on biomarkers are mainly based on what is published from their sources such as press releases, newsletters, authorities and other horizon scanning parties.

In France, the developed HS database encompasses different data on biomarkers such as the name, the biomarker usage in the clinical trial, various information on the related gene and the molecular anomaly if relevant, the methodology used to test the biomarker, the potential FDA approved tests for this biomarker and so on.

The Danish horizon scanning does not systematically follow biomarkers and diagnostic tests.

4.2.3.2 Specificities to collect and assess data on biomarkers

In Norway, if they identify new therapies that require diagnostic tests that are not common in clinical practice, the HS team searches for additional literature concerning these tests to ensure simultaneous implementation of the medicine and the diagnostic test. The Norwegian

Institute of Public Health is then responsible for early alerts and health technology assessments for medical devices, including diagnostic tests.

In France, if therapies requiring diagnostic tests that are not yet deployed in the network of cancer genetic molecular platforms are identified, INCa implements programs to enable the platforms to validate and deploy the new diagnostic tests.

Overall, it appears very important to anticipate as early as possible potential biomarker expression, on which indications could depend, to ensure the simultaneous implementation of the medicine and the diagnostic test.

4.2.4 Specificities for the pediatric population

Among the 9 organizations providing a reply to the questionnaire, two did not include pediatric indications in the scope of their HSS.

It seems that most of the HSS are treating all indications regardless of the age of the treatment population.

In the French method of scoring for prioritization, a specific score is attributed for drugs having a pediatric indication, giving more weight to clinical development in such population of patients.

In Norway, in some cases, the method for assessment of impact could be different. They sometimes treat new indications that include pediatric patients differently. For instance, they might do a simpler health technology assessment if the drug is already in use in adults, and get a new indication including children.

4.3 Anticipation of innovative therapies in oncology: remaining challenges and perspectives

4.3.1 Results of the retrospective analysis: strength of existing systems and difficulties encountered for the anticipation of innovative therapies in oncology

The results of the retrospective analysis conducted for the 11 selected indications (see details in part 3.4.1) are presented in this part gathering results from the questionnaire and from the review of HS reports publicly published.

4.3.1.1 General comments

As many of the HSS participating in the survey were implemented quite recently, it was hard to obtain clear results regarding the efficiency to identify previously marketed therapies.

Another difficulty encountered for the analysis was that most of the organizations implementing HSS do not assess the impact of a new therapy themselves: they often provide briefing/alert reports to another entity that perform the assessment.

Therefore, only few organizations were able to perform the self-assessment regarding the estimation of impact of the new indications.

The date of implementation of HSS could also affect the challenges encountered for the identification and assessment of selected indications. Countries where HSS have been implemented for a long time can have indeed a better idea of challenges encountered.

The WP9 identified 5 organizations which had publicly published information from HSS for at least one of the 11 indications screened:

- the National Institute for Health Research Innovation Observatory from the Newcastle University in England: http://www.io.nihr.ac.uk/;
- the UK NHS Specialist Pharmacy services: https://www.sps.nhs.uk/category/new-medicines/;
- the Ludwig Boltzmann institute from Austria: https://hta.lbg.ac.at/page/horizon-scanning-in-der-onkologie-berichte/en;
- the National Healthcare Institute from the Netherlands: https://www.horizonscangeneesmiddelen.nl/geneesmiddelen;
- MedNytt from the Norwegian Medicines Agency: https://www.helsebiblioteket.no/mednytt.

4.3.1.2 Anticipation of indications with high clinical added value

Overall, the indications of anti-PD-1 with high clinical added value were quite well identified by HSS prior their arrival on the market.

Through the questionnaire results, organizations estimated that the impact of these new therapies/indications and potential associated challenges were quite well anticipated. This shows that when a new therapy has a strong clinical impact, it is easier to identify it via a HS system.

Similar results were observed with the review of HS reports as these indications had been detected in the different HS with information available in English. Time for publication on websites prior marketing authorization varied a lot (from 31 months before to 2 months before).

One of the challenges highlighted for innovative immunotherapies, and especially for checkpoint inhibitors, was the difficulty to identify new relevant indications among the very broad clinical development. One of the organizations in charge of a HS system commented in their questionnaire reply that for checkpoint inhibitors, it could be difficult differing one indication from another, differing the line of therapy, and monotherapy versus combination. Indeed, there are many ongoing clinical trials with checkpoint inhibitors in most of the existing cancer localizations with slightly different objectives and designs.

4.3.1.3 Anticipation of gene and cell therapies, with the examples of CAR-T cells

The 3 indications of CAR-T cells were identified prior the granting of their marketing authorizations by most of the HSS answering the survey. However, several difficulties were highlighted regarding the assessment of impact of these therapies.

For CAR-T cells, challenges to anticipate which criteria should be used for the reimbursement of these therapies were raised.

Furthermore, the selection of centers where the therapy could be administered was also pointed out as a challenging parameter to be anticipated. Another HSS holder also raised the difficulty to foresee the complications around certifications of clinics.

At the time of the collection of survey replies, it seems that CAR-T cells were not available in Portugal and that no centers were involved regarding the use of these therapies. It was thus not possible for the Portuguese Institute of Oncology of Coimbra Francisco Gentil to anticipate the arrival of these therapies.

The WP9 had found information published from HSS on CAR-T cells on the websites of 3 out of the 5 organizations screened. Here again, the time of publication of HS reports varied from 7 months to 18.5 months prior granting of the European MA. Regarding the impact on health and social care services, one organization pointed out in their HS report that there would be a need for “new staff training requirements and requirement for new facilities”. Uncertainties regarding the cost and the economic impact were also raised.

4.3.1.4 Anticipation of indications depending on the expression of a biomarker

Whereas most of the 4 indications associated with the expression of a biomarker included in the analysis were correctly anticipated, the accompanying companion test was not always identified. For these 4 indications, the auto-evaluation performed by the organizations showed that some aspects might not have been completely anticipated prior arrival on the market.

From the review of HS report published, it appeared that information regarding potential companion diagnostic tests varied a lot across reports (from no reference to detailed references). Very rarely reports were published to anticipate the evolution of labelling in MA when it impacted the expression of a biomarker.

One of the difficulties raised was the level of expression which would be expected in the final marketing authorization. Indeed, the initial labels for 3 out of the 4 indications assessed in this category were initially not depending on any companion test; labeling evolved after to include the necessity for tumors cells to express a certain level of PD-L1.

It was highlighted in the discussion of the Ludwig Boltzmann institute HS report on Pembrolizumab in previously treated advanced NSCLC that the questions in regard to the

exact cut-off value of PD-L1-expression was remaining. Defining threshold to be considered for biomarker expression was thus identified as a very difficult parameter to anticipate in data reviewed in HSS.

Another difficulty expressed was to anticipate in which hospitals or centers the biomarker expression test could be performed.

4.3.2 Remaining challenges and perspectives to enable an efficient anticipation of innovative therapies in oncology

4.3.2.1 Drug development landscape

During the first WP9 task 3 meeting, experts highlighted that the paradigm of drug development was evolving, especially in oncology, introducing challenges which could be linked with the following issues:

- increasing total number of cancer medicines approved per year;
- more and more oncology drugs are approved with expedited programs;
- level and quality of data is poorer;
- smaller population size;
- more conditional authorization;
- use of different endpoints: more and more drugs are approved with results of Objective Response Rate (ORR) instead of Overall Survival (OS);
- innovation of novel complex trials, and single arm non-comparative trials;
- more uncertainties.

4.3.2.2 Goals and stakeholders' expectations of horizon scanning systems

Expectations from an HSS vary across stakeholders. For instance, experts consulted provided some examples of expectations from HSS for HTA agencies:

- preparedness;
- help to anticipate scientific advice requests from industries;
- help to anticipation eventual need for adaptation/evolution of system in place;
- anticipate new type, new designs of studies (example with basket and umbrella trials);
- anticipate need for new expertise;
- help to make sure that methods used to assess effectiveness are fit-for-purpose.

For other types of organizations, HSS can also be a good support to facilitate the implementation of a new treatment in a specific early access program.

4.3.2.3 Time frames

Defining the **time horizon** in a HSS remains a difficult step: the identification of an upcoming clinically impacting medicine should be made as early as possible but should include sufficient robust clinical data to be exploited. Indeed, time frames decided for HSS have a strong impact regarding available data on a specific innovative drug. For instance, HSS that identify new medicines only a few months before the marketing authorization would be based on data quite similar to ones used for the marketing authorization. On the opposite, when HSS aimed to anticipate medicines more than 3 years prior marketing authorization, available data are less certain. The earlier the assessment report is published, the harder it is to get reliable information. It triggers differences within the content of HSS outputs.

There are numerous examples of new innovative and clinically meaningful medicines gaining market authorization based on early clinical data (i.e phase II results), which makes it even more difficult for HSS to capture them in a timely manner. For instance, the marketing authorization of the two commercialized CAR-T cells had been approved based on the results of phase II pivotal trials.

Time horizon also depends on the level of information required by stakeholders, triggering the need to adapt the methodology and content of HSS output for each different stakeholder.

It was also highlighted that for the European Medicines Agency, information that could be used for HS may become available before scientific advice requests: pharmaceutical companies can share information on their pipelines and general development problems associated with their new products/new ways of manufacturing ahead of time.

4.3.2.4 Identification

Innovative medicines with a new mechanism of action are often the ones for which it is the most difficult to properly anticipate related challenges. Paradoxically, they are also the most important to catch in HSS. Indeed, first in class medicines seem to be the hardest to identify, but they are also the most important to anticipate because they can have stronger clinical, economic and organizational impacts.

Having a **structured database and automated steps** in the HSS process seems to help in the process of anticipating innovative therapies, especially when the clinical development is very broad. Indeed, it enables the possibility to generate ad hoc queries upon thematic demands and to structure data already reviewed. The NIHR IO for instance was able to generate specific ad hoc queries on their database to answer requests from the NICE regarding Advanced Therapy Medicinal Products (ATMPs) and tumour-agnostic treatments.

4.3.2.5 Filtration and prioritization

Practices and methods for the filtration and for the prioritization steps vary a lot across HSS and are not performed by all HSS holders. These steps can however be helpful in order to identify the most clinically impacting drugs among the large clinical development. It appears important to **involve relevant practicing healthcare professionals at these stages of the process**. For instance, the specific prioritization methods developed by INCa and by the Ludwig Boltzmann Institute strongly rely on the expertise from practicing healthcare professionals.

At the first WP9 task 3 meeting, it was mentioned that CAR-T cells would be an interesting model for the evaluation of HSS as 2 have been recently launched, but many more are under development: the prioritization would help to identify future CAR-T of main interest.

Specific scoring method for prioritization can also be helpful to increase the visibility of clinical development for certain population as it has been done in the INCa HSS for pediatric population.

4.3.2.6 Anticipation of impacts

Anticipation of clinical impacts

The difficulty to assess the clinical impacts of anticancer drug was underlined. This is judged to be notably due to the nature of clinical data usually available for innovative therapies (non-comparative studies, immature data, and earlier studies for authorization). Moreover, the heterogeneity of cancer drugs available and in development make it difficult to have a reproducible model for assessment of impacts. There is currently no best method to assess clinical impacts of innovative therapies in HSS.

Development of adapted methodological tools to better assess the clinical impact of innovative medicines specific to HSS appears thus essential. The Ludwig Boltzmann Institute has been using the ESMO-MCBS tool as a way to assess the impact of innovative solid tumor drugs. This works for HSS that aims at anticipating innovative therapies close to the MA. However, for horizon scanning that aimed at anticipating new therapies several years prior to approval by the regulatory authorities, data are often immature and non-comparative, so adapted tools should be developed. Scoring methods, such as the one developed by INCa, integrating the therapeutic added value according to the principal outcome and to the existence of comparator could help to better assess the potential impact of a new therapy on clinical therapeutic strategies.

The line of treatment in oncology is an essential parameter to consider in order to properly anticipate the **place of the innovative therapy in the cancer treatment strategies.** However, the anticipation of the line of treatment is still seen as a difficult step at an earlier stage of HSS. Available worldwide clinical practice guidelines can help identifying alternative therapies, but further adapted methods should be further developed. Regular pipeline meetings implemented by AMGROS with pharmaceutical industries in Denmark has helped them to increase knowledge on this aspect. Yet, it remains difficult to define how the pharmaceutical industry can be involved in the process of HSS without hindering the ethics of the implemented HSS and without limiting the publication of HSS outputs due to potential confidential data.

Anticipation of economic impacts

Economic impacts of innovative therapies are also seen as challenging to anticipate, especially due to confidentiality of data and price negotiations. Undisclosed prices of medicines make it more difficult to plan for an introduction within the health care system. The launch sequences organized by pharmaceutical industries are usually well framed. Prices defined in the first countries, where the new medicine is approved, are usually helpful to anticipate the price point in other countries. Yet, the negotiations of prices in countries where the new drug is first launched usually have a strong impact for future negotiations in smaller countries. According to experts attending our meetings, compared to American prices, the prices of innovative therapies in Canada often appear to be closer to European prices.

Moreover, budget assessment can be very specific to one country, making it hard to develop models to anticipate economic challenges.

Anticipation of organizational impacts

Challenges related to the production and supply of innovative therapies remain difficult to anticipate. Yet, understanding production steps and supply chain organization related to innovative therapies as early as possible in the development process enables a better anticipation of potential related impacts on healthcare system, especially regarding organization of care. Pipeline meetings with pharmaceutical companies have been seen as a good solution to get further information on these aspects. Indeed, pharmaceutical industries become familiar with these difficulties encountered at a very early stage of the clinical development.

The difficulty to anticipate the **selection and certification of centers** where these new therapies could be administered was also raised, especially for CAR-T cells. Having a strong communication between all stakeholders involved on the territory before the marketing authorization, appears thus as a necessity to facilitate the implementation of these therapies in clinical practices.

Finally, foresee new technologies which could have an impact on drug development appear also very important. For instance, for gene and cell therapies, the anticipation of potential related **new technologies**, such as genome editing methods, is of major interest because it can have a direct impact on future available therapies and on their production. This might lead to the need to collect and review additional data not directly linked to the clinical trials.

4.3.2.7 Dissemination

Overall, publication of HSS outputs remains limited: in order to **reduce potential inequities in Europe regarding the anticipation of upcoming marketing authorization** of innovative therapies, it can be very helpful to **share common tools** and to **make HSS outputs publicly available whenever possible.** At the iPAAC second task 3 meeting, several canals for sharing knowledge were suggested by experts consulted such as WHO and EuroScan. Some horizon scanning systems also publish outputs publicly on their website. For instance, the HSS in Denmark, Austria, Netherlands, UK and Norway have several outputs published on their website, most of the time in national language, but AMGROS and the Ludwig Boltzmann institute also publishes some information related to their HSS in English. Furthermore, early 2020, the EUnetHTA network has published a list of prioritized topics to enable joint assessment. This is a way to share priorities among European member states.

The timing and HSS outputs/alert reports should also be relevant to enable the implementation of **early access programs** when possible. More generally, disseminating the results between all relevant actors in charge of the evaluation and of the financing of anticancer drugs is important to promote exchange and inter-institutional discussions around upcoming innovative therapies to facilitate their dissemination on the territory.

Following the presentation from NIHR IO on ad hoc queries performed on their HS database following specific thematic requests from stakeholders, several experts underlined their interest of performing such reviews of available data on a specific theme. It was underlined that for small countries, it could be difficult to perform such detailed reviews of ongoing clinical

trials, especially due to limited resources. Thus, the importance to share results from this kind of research was raised.

Another challenge pointed out was the need to better define how to involve pharmaceutical industries in HSS processes without being detrimental regarding the ethic and rules of deontology of the process. Intellectual property and confidentiality of data provided should be ensured in the HSS process. Nevertheless, confidential data should not be seen as a limit to publish HSS briefing reports, even though published HSS reports might need to be adapted to ensure that only public data are provided.

An additional question was raised: how can we overcome the gap between confidential data such as that provided to the EMA or National competent authorities for early anticipation of new and emerging innovative therapies and the need to have public information in horizon scanning systems?

Finally, there is a need to continue to **strengthen existing collaborations and initiatives** on HSS. The long-standing network EuroScan has been a very useful source of methodological tools for several organizations, which have implemented horizon scanning systems to anticipate innovative therapies. It is also the occasion to share expertise among a common network. The EUnetHTA network is also an example of collaboration among HTA agencies on activities related to HSS. Eventually, the International Horizon Scanning Initiative (IHSI) has been recently set up and aims at building an horizon scanning systems for which the database would be shared between the involved member states. The public tender had been launched in February 2020 to determine the service provider.

5 Conclusion

Horizon scanning systems are seen as the foundation supporting health technology agencies, but also other public health and medicine agencies, policy makers or healthcare professionals for the proper introduction and diffusion of innovative drugs on the territory. Considering the significant part of oncology in upcoming innovations, HSS are key elements for this therapeutic field, where numerous innovative therapies reach the market. It is thus important to have efficient systems to better anticipate innovative therapies in cancer.

There is currently a minority of HSS specific to oncology. Yet, most of the experts involved in this iPAAC WP9 task 3 work seemed to agree that this therapeutic field would benefit from specific considerations, especially in the light of the variety of drugs and classes available, the earliness of data supporting marketing authorization and the dynamics of this therapeutic area. Given that data can broadly differ depending on the cancer incidence, on available treatments and on the severity of cancer, specificities could also be considered across cancer types.

Several HS organizations highlighted the need to adapt their methodology for the anticipation of gene and cell therapies, with for instance the necessity to screen early phase clinical trials or to collect additional data to be sure to detect these clinically impacting therapies prior their arrival on the market. For CAR-T cells, understanding the production and supply steps appeared as essential to properly anticipate their organizational impacts.

Besides, it is also important to identify as early as possible potential biomarker expression, on which indications could depend, to ensure the simultaneous implementation of the medicine and the diagnostic test. In some cases, this might imply the collection of additional information. Expected biomarker expression threshold in the final approved marketing authorization as well as centers able to perform the diagnostic tests conditioning the prescription seemed to be the hardest parameters to anticipate.

Several perspectives had been foreseen to improve the anticipation of impacts of innovative anticancer drugs in HS process. For instance, having a structured database was seen as helpful for the identification step, as it allowed the generation of ad hoc queries. Involving the expertise of practicing clinicians brings also a strong support for prioritizing and predicting clinically impacting drugs. Developing methodological tools such as assessment scales or scoring method adapted to anticancer drugs had also been suggested. Finally, pipeline meetings with pharmaceutical industries were seen as a valuable resource to better anticipate the place of the new treatment in therapeutic strategies and potential challenges related to production and supply which were particularly difficult to anticipate for gene and cell therapies such as CAR-T cells. Yet, it remains complex to define how to involve pharmaceutical industries in the process of HSS without hindering the ethics of the implemented HSS and without limiting the publication of HSS output due notably to confidential data.

Disseminating HSS results between all relevant actors in charge of the evaluation and of the financing of anticancer drugs is important to promote exchange and inter-institutional discussions around upcoming innovative therapies to facilitate their introduction on the territory. In order to reduce potential inequities in Europe, it would be very valuable to increase knowledge by sharing common tools, to make HSS outputs publicly available whenever possible and to continue to strengthen existing collaborations and initiatives on HSS.

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7 Appendices

7.1 Meeting minutes from the WP9 task 3 meeting – 06 March 2019 – Brussels (Sciensano)

iPAAC
INNOVATIVE PARTNERSHIP
FOR ACTION AGAINST CANCER

Meeting minutes

Title:	WP9 task 2 - 3 meeting : Horizon scanning systems and biomarkers
Purpose:	Discussion on horizon scanning systems (HSS) and biomarkers
Date and time:	06 March 2019
Location:	Sciensano, Ernest Blérot 1, Brussels, Belgium

Attendees

Name	Organisation (department, division)
Bermudez Elisabeth	Medicines Department, INCa, France
Berraondo Pedro	CIBERONC, Spain
Denis Helene	Project manager, Medicines Department, INCa, France
Drochon Anne	INC, Luxembourg
Groessman Nicole	Ludwig Boltzmann institute, Austria
Hébrant Aline	Sciensano, Belgium
Herold Ralph	EMA, UK
Joppi Roberta	EUROSCAN, Italy
Kozhaeva Olga	European Society for Paediatric Oncology – SIOPE
Laurinavičius Arvydas	Vilnius University Hospital Santaros Klinikos, Lithuania
Maignen François	NICE, UK
Negellen Sophie	Head of the Medicines Department, INCa, France
Nowak Frédérique	Head of Biology, Transfer and Innovations Department, INCa, France
Prokupkova Anna	ECL, Belgium
Speksnijder Niels	IHSI, Netherlands
Van Den Bulcke Marc	Sciensano, Belgium
Vassal Gilles	European Society for Paediatric Oncology – SIOPE

Decisions made

What and why was decided, what impacts are expected
1. *Content and timelines of the questionnaire* A questionnaire was suggested by the WP9 in order to highlight eventual specificities for HSS in terms of methodology for oncology, and more particularly for gene and cell therapies as well as for biomarkers. The questionnaire will be adapted with comments gathered from the meeting, especially to give more room to difficulties encountered for the assessment of impact of innovative therapies in the field of oncology, which seems to be the most challenging issue. It will be sent by email for final validation prior dissemination. The questionnaire will then be disseminated to persons closely involved in HSS methodology and results will be collected until October. Phone interviews could be organized to facilitate the collection of replies. 2. *Next meeting to be organized on the thematic of HSS* It was suggested to have another meeting to continue the discussion on this thematic. INCa offered to organize the meeting in their building. Post-meeting note: INCa could organize this meeting in November (one day to be chosen in the

week from November 18th to 22nd)

3. *Point of interests for the roadmap*

For the roadmap, the WP9 suggested to include:

- Definition and purposes of Horizon scanning systems
- Main methodological steps to follow to implement an horizon scanning system
- Present one or two existing HS systems
- Present the main ongoing collaboration initiatives
- Present specificities to be considered in the HS methodology for the oncology field with a focus on innovative immunotherapies, gene and cell therapies (with the example of CAR-T cells) and biomarkers
- Highlight challenges related to the assessment of impact of innovative therapies in the field of oncology

Discussion

Items or knowledge to be shared

Introduction

It was announced that Muriel Dahan had left INCa since March 1st. The medicines department, with the support of INCa direction, will ensure the continuity of the work while her replacement is hired.

The main goals and organization of the joint action were reminded.

Horizon Scanning Systems

See related presentation (Helene Denis/Sophie Negellen).

Introduction regarding HSS objectives and definition was provided.
Goals, timelines, milestones and methodology of the iPAAC WP9 task 3 were reminded.

French HSS

See related presentation (Elisabeth Bermudez/Sophie Negellen)

The term "prioritization" was clarified: it is a term usually used in the horizon scanning methodology. The judgement performed to "prioritize" drugs will be based on scoring method to be more neutral.

Clarifications were requested concerning stakeholders and target population of assessment reports. INCa reminded that there is a will to inform policy makers/payers to anticipate costs and organization of care, but also to inform healthcare professional and patients about potential new therapeutic options (health democracy). It will also help INCa for its internal activities (for instance to help identifying the need for a new or for an update of clinical practice guidelines).

SIOPE mentioned that CAR-T cells will be an interesting model for the evaluation of HSS: 2 have been recently launched, but much more are under development. The prioritization will help to

identify CAR-T of main interest.

Comment from ECL:
HSS appear to be a good supportive tool for policy makers.
How do we see further collaboration in this field?

- ⇨ Examples of collaborations will be provided with Euroscan, IHSI and EUnetHTA
- ⇨ The first step is to get a common understanding of these tools and their methodology

Innovation observatory from Newcastle university

Apologies from Dawn Craig who could not attend the meeting in person. Her slides presenting the Innovation observatory from Newcastle university were provided in the meeting material.

NICE perspective on HSS

See related presentation (François Maignen).

The UK system is mainly based on the voluntary completion of the Pharmascan database by pharmaceutical industries; but this is not the only source of information. To the NICE point of view, it is an added value to obtain clinical results on drugs.

Expectations of NICE from HSS:

- preparedness
- Help to anticipate scientific advice requests from industries
- Help to anticipation eventual need for adaptation/evolution of system in place
- Anticipate new type, new designs of studies (example with basket and umbrella trials)
- Anticipate need for new expertise
- Help to make sure that methods used to assess effectiveness are fit-for-purpose

Budget assessment: can be very specific to one country: hard to have models
With the example of targeted therapies, NICE underlined the difficulties to assess the impact of anticancer drug due to the nature of clinical data (non-comparative studies, immature data).

Ludwig Boltzmann institute HSS

See related presentation (Nicole Groessman).

Important to define the following parameters prior implementing a HSS:

1) Stakeholders/Target of the HHS
2) Timelines expected

Some characteristics of this HSS:

- One scientific publication is needed for a drug/indication to be filtered
- Pediatry is not on the scope of this HSS
- Dissemination ++: posting of all evaluation reports on the website in English + emailing
- No clear collaboration between this HSS and the national HTA agency

HSS from Netherlands

See related presentation (Niels Speksnijder)

In addition to the slides, the following information were provided :

- Started by the ministry of health in 2015 and transferred to the National healthcare institute in 2017.
- Division in 7 therapeutic domains. There is one expert group for each of these 7 domains including clinicians. Disclosure of conflict of interests is mandatory for clinicians involved in these groups.
- One paediatrician is involved for relevant indications.
- Expected costs are available online
- Scan stops when decision for reimbursement is taken (not when the drug is approved).
- About 400 drugs/extensions of indications on the website now.
- Interaction with pharma industries: no formalized way. Usually an Excel table is sent to them and they can provide their data. About 75% of manufacturers provide information. No face-to-face meetings.
- Time frame: 2 years prior marketing authorization
- Usually include phase III trials (but also phase II if PRIME Scheme)
- This HS also provides information on patent rights.
- Scope: only pharmaceuticals
- No published information on potential associated biomarkers. Another organization in the Netherlands is working more closely on these aspects (Hartwig Medical Foundation), but they do not publish public information.

IHSI

See related presentation (Niels Speksnijder)

Ongoing project to build a collaborative international HSS

Italian HSS

See related presentation (Roberta Joppi)

Outputs could also be used for early assessment

The difficulty to assess the impacts of anticancer drug is underlined.
This is due to the nature of clinical data (earlier studies for authorization).
Moreover, it is difficult to have a model for this assessment due to the heterogeneity of drugs.

Euroscan

See related presentation (Roberta Joppi)

Main characteristics:

- Started in the mid-1990
- Toolkit available online to support member states
- Goal is to continue to develop such methodological tools.

The value to have international countries included in this network is to strengthen methodological tools with experiences from each country having an HSS.

The database used in Euroscan is mainly used to share information (nothing formalized or structured).

Other ongoing initiatives on HSS

See related presentation (Helene Denis)

In view of the current work on Horizon Scanning systems, EUnetHTA was invited but could not be represented for this meeting. A post-meeting TC will be organized with Chantal Bélorgey (vice chair EUnetHTA).

Presentation of the retrospective study conducted with the aim to discuss eventual specificities in the field of oncology and more particularly gene and cell therapies as well as biomarkers.

Paradigm to develop drugs is changing:

- more and more drugs are approved with expedited programs
- level and quality of data is poorer
- smaller population size
- more conditional authorization
- use of surrogate endpoints (more and more drugs are approved with results of Objective Response Rate (ORR) instead of Overall Survival (OS))
- changing designs of clinical trials
- more uncertainties

Some suggestions :

- Better tools are needed to support the assessment of innovative therapies in the context of this changing landscape.
- Need to also foresee new technologies which could have an impact on drug development
- Modifying our methods
- Implementation of early access scheme in relation with impact assessment report from HSS
- Tools needed to better assess the organization of care (e.g. for CAR-T cells: it was hard to anticipate far in advance)
- Better anticipation of new expertise needed.

Hard to define the best time frames for HSS: depends a lot from stakeholders. The earlier the assessment report is published, the harder it is to get reliable information.

EMA: HS start before scientific advice requests: invitation of industries to share their pipelines and problematics associated with their new products/new ways of manufacturing ahead of time.

Overall, concerning specificities of HS methodology in the oncology field, it seems that there are no specific criteria needed for identification, but maybe improvement could be done at the prioritization level, and more importantly, better tools are needed for the assessment of impact.

Results of task 1

It was decided to skip this part in order to have more time for the discussion on HSS.
The PowerPoint presentation was provided to persons attending the meeting. It will be later shared among all partners.

Biomarkers

See related presentation (Frédérique Nowak)

Presentation of the comparison of marketing authorization conditioned by a biomarker expression and guidelines recommendations.

Most of the off-label recommendations identified were for MSI-H in colorectal cancer.

Tumor mutational burden
Currently not implemented in current practices. Risk for strong impact on organization of care/ healthcare systems as this test is not currently used ➔ important to be anticipated with HSS

It was suggested to organize an additional questionnaire to get better understanding of the management of genomics associated with oncology in European countries.
However, it appears hard to get deep feedback information through the questionnaire, especially as differences are observed between hospitals within a same country.
Suggestion to focus on a few countries rather than to try to have exhaustive but incomplete information. For the roadmap, examples of the functioning a few countries could be taken as examples.

To be further discussed.

7.2 Meeting minutes from the WP9 task 3 meeting – 18 November 2019 – Boulogne Billancourt (INCa)

Meeting minutes

Title:	WP9 task 3 meeting : Horizon scanning systems
Purpose:	Discussion on horizon scanning systems (HSS) applied for Cancer control in Europe
Date and time:	18 November 2019
Location:	INCa, 52 avenue André Morizet, 92513 Boulogne-Billancourt CEDEX

Attendees

Name	Organisation (department, division)
BERMUDEZ Elisabeth	Medicines Department, INCa, FRANCE
BEHNK Trine Ann	AMGROS - DENMARK
BORRAS Josep M	University of Barcelona | UB · Department of Clinical Sciences - SPAIN
BRÄUNER Helle	AMGROS - DENMARK
DENIS Helene	Medicines Department, INCa, FRANCE
FAIRBAIRN Ross	NIHR Innovation Observatory Newcastle University
GABRIELE Lucia	Department of Oncology and Molecular Medicine - Istituto Superiore di Sanità, Rome, ITALY
GROESSMAN Nicole	Ludwig Boltzmann institute, AUSTRIA
KROL Aurélie	Department of Biology, Transfer and Innovations INCa - FRANCE
LAUVRAK Vigdis	Norwegian Institute of Public Health - EUnetHTA - NORWAY
MARINHEIRO Bernardo	European Society for Paediatric Oncology (SIOPE)
MILOSAVLJEVIC Neda	Clinical Center of Kragujevac, SERBIA
NEGELLEN Sophie	Medicines advisor & Head of the Medicines Department, INCa, FRANCE
OGUNBAYO Dapo	NIHR Innovation observatory, Newcastle University, UK
VAN DEN BULCKE Marc	Sciensano, BELGIUM
WAEYTENS Anouk	Sciensano, BELGIUM

Decisions made

What and why was decided, what impacts are expected
1. *Involvement of partners and experts for the writing of the task 3 deliverables as well as for providing input for the roadmap* WP9 Partners and experts are invited to review the initial draft version of the deliverable linked to the task 3 and to complete it with their own experience and specificities of their own systems. They were also invited to think about potential One-pagers that they would be interested to develop for the iPAAC roadmap. 2. *Remaining challenges* Specificities to be considered in horizon scanning systems to enable a proper anticipation of innovative therapies and their potential associated clinical, economic and organizational impacts in the field of oncology have been highlighted. Based on the meeting discussions (from 6 March

2019 and 18 November 2019) and results of the study conducted by the WP9, a list of the main challenges remaining in this field has been compiled by the WP9.
The WP9 partners and experts are asked to review, complete and validate this list.

3. iPAAC WP9 task 3 deliverables

As previously suggested at the past WP9 meeting, the task 3 deliverable will contain the following information:

- Definition and purposes of Horizon scanning systems
- Main methodological steps to follow to implement an horizon scanning system
- Overview of existing HS systems in Europe
- Main ongoing collaboration initiatives in this field
- Specificities to be considered in the HS methodology for the oncology field with a focus on innovative immunotherapies, gene and cell therapies and biomarkers
- Remaining challenges related to the assessment of impact of innovative therapies in the field of oncology

In addition, some One-pagers will be suggested by the WP9 partners and experts to be included in the iPAAC roadmap.

Discussion

Items or knowledge to be shared

Introduction

Sophie Negellen, WP9 leader, mentioned the main goals and the context of the iPAAC joint action, and more especially regarding the WP9 on innovative therapies in cancer.

Presentation of iPAAC survey results conducted by INCa: specificities in HSS for oncology medicines

See related presentation from Helene Denis, INCa, France

Previous steps of the task 3 work were reminded.
The main results of the WP9 study conducted among HSS holders were presented.

Comments provided:

The date of implementation of HSS can affect the challenges encountered for the identification and assessment of selected indications. Countries where HSS have been implemented for a long time can have indeed a better idea of challenges encountered.

Data availability can vary depending on cancer types. For instance, it is easier to obtain comparative data in large spread cancer such as prostate and breast cancer, whereas in hematologic cancer for instance, it might be harder. Thus, specificities might also need to be considered depending on the cancer type.

Innovative medicines with a new mechanism of action are often the ones for which it is the most

difficult to properly anticipate related challenges. Paradoxically, they are also the most important to catch in HSS.

There is no best method to assess clinical impacts of innovative therapies in HSS. Worldwide clinical practice guidelines available can help identifying alternative therapies. However, anticipation of the line of treatment is still seen as a difficult step at earlier stage of HSS. It appears thus very important to involve healthcare professional and learned societies in the process of HSS in order to obtain a good understanding of challenges encountered at the hospitals/medical centers level. Clinicians are seen as the best source of information regarding alternative treatments available and in development in each country.

Time horizon / time frame decided for horizon scanning systems also have a strong impact regarding available data on a specific innovative drug. For instance, HSS that identify new medicines a few months before the marketing authorization would have comparable data on benefit/risk than the medicine authority deciding on the attribution of the marketing authorization. On the opposite, when HSS aimed to anticipate medicines more than 3 years prior marketing authorization, available data are less consequent. It triggers differences within the content of HSS outputs.

It appears important to obtain a good understanding of production steps and supply chain organization related to innovative therapies as early as possible in the development process to better anticipate potential related impacts on healthcare system, especially regarding organization of care. Concerning gene and cell therapies, it is of main interest to identify the site of production of these drugs to better anticipate their arrival on the market.

The organization of pipelines meeting with pharmaceutical industries was suggested as a way to anticipate challenges related to production and supply of innovative therapies as well as to get a better idea of the line of treatment expected for the innovative therapy. One of the challenges pointed out was to better define how to involve pharmaceutical industries in HSS processes without being detrimental regarding the ethic and rules of deontology of the process. Intellectual property and confidentiality of data provided should be ensured in the HSS process. Nevertheless, confidential data should not be seen as a limit to publish HSS briefing reports, even though published HSS reports might need to be adapted to ensure that only public data are provided.
It was also specified that including head offices (rather than local offices) in pipeline meetings are usually more helpful to obtain data regarding long-term strategies, which is specifically interesting for HSS with a time horizon at 3 years or more prior marketing authorization.

Regarding the anticipation of potential economic challenges related to innovative therapies, it was specified that it is usually difficult to obtain economic data at pipeline meetings as pharmaceutical industries are not always willing to provide information on these aspects. US prices, Canadian prices and prices in the first EU countries where the new medicine is approved are usually helpful to anticipate these challenges. Literature on the topic exists (to be provided by AMGROS).

<u>Presentation of the iPAAC Roadmap</u>

See related presentation from Marc Van Den Bulcke, Sciensano, Belgium

The iPAAC report for the European Commission should focus on the work conducted by the joint action, and more especially on:

- Innovative aspects
- Implementation
- Sustainability

The current political context at the European Commission level is to be followed for potential impact on the iPAAC joint action: a European cancer plan is under development (under the umbrella of DG Santé) and a mission on cancer has been launched (under the umbrella of DG research).

Integration and valorisation of task 3 work on HSS in the iPAAC roadmap

WP9 partners and experts are invited to think about potential One-pagers that they would be interested to develop to integrate within the iPAAC roadmap.
Suggestion: think about specificity, an innovative approach implemented in existing HSS which should be highlighted in One-pagers.
Some examples were provided:

- The scoring method of the INCa HSS: mobilization of healthcare professionals through learned societies to better select future clinically impacting innovative medicines
- European collaboration, such as EuroScan, IHSI, EUnetHTA

An explanatory note will be provided by the WP4 regarding how to complete a One-pager.

It was specified that the content of these One-pagers should be focusing on the policy implemented rather than on research and results obtain thanks to the policy implemented. This would be more relevant for the iPAAC roadmap.

Additional comments:

Difficulties to negotiate prices of innovative therapies in small countries were highlighted.
The launch sequences organized by pharmaceutical industries are usually clear and the first negotiations of prices in countries were the new drug is first launched have a strong impact for future negotiations in smaller countries.

Early identification of tumour-agnostic treatments via horizon scanning – opportunities and challenges

See related presentation from Dapo Ogunbayo, NIHR Innovation Observatory, UK

The NIHR IO currently includes clinical trials occurring in Europe and in the United States in the scope of their HSS.
It was mentioned that it could be interesting to broaden the scope to clinical trials occurring in other additional countries.

NIHR IO tries to automate HSS steps as much as possible. Their database enables the conduct of ad hoc research upon stakeholders requests on specific topics such as the one presented at this meeting on tumour-agnostic treatment, but also on Advanced Therapy Medicinal Product (ATMP) for instance.

One question regarding the frequency of database updates was raised. NIHRIO has specific pre-defined criteria to define the period of review. It could be every 3 to 6 months for drugs with a status in "monitoring". The team is also alerted upon significant scientific press release.

Some experts underlined their interest in such data. It was also underlined that for small countries, it could be difficult to perform such detailed studies/reviews of ongoing clinical trials. The importance to share this kind of data was raised. Several canals were suggested such as WHO, and EuroScan.

INCa scoring method and mobilization of stakeholders as support to prioritize and to better select future impacting innovative therapies

See related presentation from Elisabeth Bermudez, INCa, France

Some clarifications were provided following questions from the assembly:

- Stakeholders involved in the process of prioritization are healthcare professionals (HCP) contacted through relevant French learned societies. Patient associations and industries are not involved in the French HSS process.
- The 2 scores attributed in this method, 1 from HCP and 1 from INCa are both weighted similarly (50/50). The score attributed by INCa is based on specific criteria to avoid partial judgment as much as possible.
- There are no criteria to be scored regarding economic parameters at the prioritization step, but research on economic data is performed for each prioritized drug.
- There is no direct link between the French HSS outputs and drugs entering early access programs in France (ATU – Autorisation temporaire d'utilisation): the decision of drugs to be included in this program is under the responsibility of the French medicines agency (called ANSM). However, the ANSM will be informed when results of INCa HSS are available. This could be helpful to identify drugs eligible for ATU or RTU.

Application of the Magnitude of Clinical Benefit Scale from the European Society of Medical Oncology to score solid tumour drugs in Horizon scanning assessment

See related presentation from Nicole Groessman, Ludwig Boltzmann Institute, Austria

Specifications:

- The ESMO-MCBS tool can be used only for solid tumours.
- Cost is not taken into account in this scale.
- This tool can also be used in subgroups but data on specific subgroups are not always available regarding quality of life and toxicities.

This tool was originally developed for drugs with a marketing authorization. It can be used in HSS aiming to identify drugs a few months prior to market launch. However, it was highlighted that they might need to develop adapted tools to better assess medicines for which data available are more premature, for instance for HSS aiming at assessing new medicines earlier.

European collaborations on HSS: expectations and challenges

See related presentation from Vigdis Lauvrak, EUnetHTA

HTA proposal for EU regulation includes some aspects on horizon scanning systems. Methods

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mentioned by EUnetHTA are included within the proposal.

There are some conflicting views among EUnetHTA members regarding the involvement of pharmaceutical industries in the process.

Final recommendations are expected for January 2020. This joint action is planned to end next year. The sustainability is questioned. Even if the European HTA proposal is implemented, there will still be a need for collaboration and network on HTA, but the status is yet to be defined.

The EFPIA position paper was referred regarding the opinion of pharmaceutical industries on horizon scanning systems.

It appears overall important to continue to strengthen collaboration in the field of horizon scanning systems.

Update on the International Horizon Scanning Initiative (IHSI) from Anouk Waeytens:

A new website has been launched: https://ihsi-health.org/

9 countries are involved: Belgium, Ireland, Netherlands, Luxembourg, Denmark, Norway, Sweden, Switzerland and Portugal.

The launch for tender is expected for February 2020. It will be published in European gazette as well as in national gazettes.

The focus will be pharmaceuticals (medical devices under discussion).

Identification, filtration and prioritization steps will be common to all countries involved. High impact reports will be produced by the service provider and should be publicly published.

This initiative is financed by member states themselves.

Countries will be able to run their own ad hoc queries in the database.
Ad hoc access to the database or to certain data against fees has not been discussed yet.

Link between HSS output and early access programs?

It was raised that originally, HSS outputs were used mainly by HTA agencies, but could be of interests for other type of stakeholders such as agencies in charge of early access programs.

It seems that currently, there is no direct link between HSS outputs and inclusion of specific innovative therapies in early access programs, but this is an aspect that might be interesting to develop in the future.

One limit was raised: in several countries, the entering of a new medicine in an early access program depends on the specific application that should be done by the industry developing the new drug.

7.3 Questions addressed to organizations in charge of a horizon scanning system

General questions

Are pediatric indications included in the scope of your horizon scanning? □ Yes □ No

Please specify if needed:

_____
_____
_____

Do you use a structured/automated database to identify drugs in development?

_____
_____
_____

How long prior marketing authorizations do you usually identify new medicines/indications?

_____
_____

Do you publicly publish Horizon Scanning Assessment reports?

□ Yes, all of them □ in English
□ Yes, some of them □ in national language
□ No

Do you publicly publish list of prioritized medicines?

□ Yes, all of them □ in English
□ Yes, some of them □ in national language
□ No

Do you use a scoring method for the prioritization steps? □ Yes □ No

If yes, please specify:

_____
_____
_____
_____

Oncology specificities

Is there any specificity for oncology medicines in your Horizon scanning? □ Yes □ No

If yes, what kind of specificities do you use?

□ Inclusion of earlier phase clinical trials

□ Collection of additional data

□ Different filtration

□ Different prioritization

□ Different method for assessment of impact

□ Other

Please specify:

_____

_____

_____

Gene and cells therapies specificities

Is there any specificity for gene and cells therapies in your Horizon Scanning System? □ Yes □ No

If yes, what kind of specificities do you use?

□ Inclusion of earlier phase clinical trials

□ Collection of additional data

□ Different filtration

□ Different prioritization

□ Different method for assessment of impact

□ Other

Please specify:

_____

_____

_____

Biomarkers specificities

Are you able to identify potential predictive biomarkers linked with new therapies (therapeutic indication depending on a biomarker expression, implementation of companion test…) ?

□ Yes □ No

If yes, what kind of information are you able to identify?

_____

_____

Is there any specificity for the assessment of potential predictive biomarkers linked with new therapies in your Horizon Scanning System?

□ Yes □ No

If yes, what kind of specificities do you use?

□ Inclusion of earlier phase clinical trials

□ Collection of additional data

□ Different filtration

□ Different prioritization

□ Different method for assessment of impact

□ Other

Please specify:

_____

_____

_____

Do you usually include information regarding relevant biomarker associated with emergent drug in your Horizon Scanning assessment reports? □ Yes □ No

Specificities for pediatric indications

Is there any specificity for the assessment of pediatric indications in your Horizon Scanning System?

□ Yes □ No

If yes, what kind of specificities do you use?

□ Inclusion of earlier phase clinical trials

□ Collection of additional data

□ Different filtration

□ Different prioritization

□ Different method for assessment of impact

□ Other

Please specify:

_____
_____
_____

Retrospective analysis

For each of the following indication, could you please provide the following information?

6) Was your system enabling the identification of this indication prior marketing authorization?
7) Reason for no identification via Horizon Scanning if applicable (e.g. methodological gap, not included in the scope, …)
8) Was an assessment report publicly published for this indication?
9) Rate the assessment report provided by your organization regarding the estimation of impact of the new indication;
10) Indicate eventual challenges encountered for the assessment of impact of this new indication.

Indications with a clinical added value considered as moderate by HAS (ASMR III)

Nivolumab (OPDIVO) as monotherapy for the treatment of advanced (unresectable or metastatic) melanoma in adults.

1) Identification via Horizon Scanning: □ Yes □ No
2) Reason for no identification via Horizon Scanning if applicable:
   _____
   _____
   _____
3) Was an assessment report publicly published for this indication?
   □ Yes □ No □ Not applicable

4) If an assessment of impact for this indication was performed by your organization, could you please rate your evaluation between 1 and 10 (10 being the best: very good anticipation of impact of this new indication, and 1 the lower: many challenges did not enabled us to correctly anticipate the impact of this indication).
   □ 1 □ 2 □ 3 □ 4 □ 5 □ 6 □ 7 □ 8 □ 9 □ 10

5) Please indicate the eventual challenges encountered for the assessment of impact of this new indication:

_____
_____
_____

Nivolumab (OPDIVO) as monotherapy for the adjuvant treatment of adults with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection:

1) Identification via Horizon Scanning: □ Yes □ No

2) Reason for no identification via Horizon Scanning if applicable:

_____

_____

_____

3) Was an assessment report publicly published for this indication?
□ Yes □ No □ Not applicable

4) If an assessment of impact for this indication was performed by your organization, could you please rate your evaluation between 1 and 10 (10 being the best: very good anticipation of impact of this new indication, and 1 the lower: many challenges did not enabled us to correctly anticipate the impact of this indication).

□ 1 □ 2 □ 3 □ 4 □ 5 □ 6 □ 7 □ 8 □ 9 □ 10

5) Please indicate the eventual challenges encountered for the assessment of impact of this new indication:

_____

_____

_____

Nivolumab (OPDIVO) as monotherapy for the treatment of advanced renal cell carcinoma after prior therapy in adults.

1) Identification via Horizon Scanning: □ Yes □ No
2) Reason for no identification via Horizon Scanning if applicable:

_____

_____

_____

3) Was an assessment report publicly published for this indication?
□ Yes □ No □ Not applicable

4) If an assessment of impact for this indication was performed by your organization, could you please rate your evaluation between 1 and 10 (10 being the best: very good anticipation of impact of this new indication, and 1 the lower: many challenges did not enabled us to correctly anticipate the impact of this indication).

□ 1 □ 2 □ 3 □ 4 □ 5 □ 6 □ 7 □ 8 □ 9 □ 10

5) Please indicate the eventual challenges encountered for the assessment of impact of this new indication:

_____

_____

_____

Nivolumab (OPDIVO) as monotherapy for locally advanced or metastatic squamous non-small cell lung cancer (NSCLC) after prior chemotherapy in adults

1) Identification via Horizon Scanning: □ Yes □ No
2) Reason for no identification via Horizon Scanning if applicable:

_____
_____
_____

3) Was an assessment report publicly published for this indication?
□ Yes □ No □ Not applicable

4) If an assessment of impact for this indication was performed by your organization, could you please rate your evaluation between 1 and 10 (10 being the best: very good anticipation of impact of this new indication, and 1 the lower: many challenges did not enabled us to correctly anticipate the impact of this indication).

□ 1 □ 2 □ 3 □ 4 □ 5 □ 6 □ 7 □ 8 □ 9 □ 10

5) Please indicate the eventual challenges encountered for the assessment of impact of this new indication:

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_____
_____

CAR-T cells approved in 2018:

Tisagenlecleucel (Kymriah) indicated for paediatric and young adult patients up to 25 years of age with B‑cell acute lymphoblastic leukaemia (ALL) that is refractory, in relapse post‑transplant or in second or later relapse.

1) Identification via Horizon Scanning: □ Yes □ No
2) Reason for no identification via Horizon Scanning if applicable:

_____
_____
_____

3) Was an assessment report publicly published for this indication?
□ Yes □ No □ Not applicable

4) If an assessment of impact for this indication was performed by your organization, could you please rate your evaluation between 1 and 10 (10 being the best: very good anticipation of impact of this new indication, and 1 the lower: many challenges did not enabled us to correctly anticipate the impact of this indication).

□ 1 □ 2 □ 3 □ 4 □ 5 □ 6 □ 7 □ 8 □ 9 □ 10

5) Please indicate the eventual challenges encountered for the assessment of impact of this new indication:

_____
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_____

Tisagenlecleucel (Kymriah)indicated for adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy

1) Identification via Horizon Scanning: □ Yes □ No
2) Reason for no identification via Horizon Scanning if applicable:

_____
_____
_____

3) Was an assessment report publicly published for this indication?
□ Yes □ No □ Not applicable

4) If an assessment of impact for this indication was performed by your organization, could you please rate your evaluation between 1 and 10 (10 being the best: very good anticipation of impact of this new indication, and 1 the lower: many challenges did not enabled us to correctly anticipate the impact of this indication).

□ 1 □ 2 □ 3 □ 4 □ 5 □ 6 □ 7 □ 8 □ 9 □ 10

5) Please indicate the eventual challenges encountered for the assessment of impact of this new indication:

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_____

Axicabtagene ciloleucel (Yescarta) indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and primary mediastinal large B-cell lymphoma (PMBCL), after two or more lines of systemic therapy.

1) Identification via Horizon Scanning: □ Yes □ No
2) Reason for no identification via Horizon Scanning if applicable:

_____
_____
_____

3) Was an assessment report publicly published for this indication?
□ Yes □ No □ Not applicable

4) If an assessment of impact for this indication was performed by your organization, could you please rate your evaluation between 1 and 10 (10 being the best: very good anticipation of impact of this new indication, and 1 the lower: many challenges did not enabled us to correctly anticipate the impact of this indication).

□ 1 □ 2 □ 3 □ 4 □ 5 □ 6 □ 7 □ 8 □ 9 □ 10

5) Please indicate the eventual challenges encountered for the assessment of impact of this new indication:

_____
_____
_____

Indications depending on the expression of a specific biomarker:

For these indications depending on the expression of a specific biomarker, we also ask you to specify if the companion test associated was anticipated with your HSS.

Pembrolizumab (Keytruda) as monotherapy for the treatment of locally advanced or metastatic NSCLC in adults whose tumours express PD-L1 with a ≥1% TPS and who have received at least one prior chemotherapy regimen. (Patients with EGFR or ALK positive tumour mutations should also have received targeted therapy before receiving KEYTRUDA.)

1) Identification via Horizon Scanning: □ Yes □ No
2) Reason for no identification via Horizon Scanning if applicable:

_____
_____
_____

3) Was an assessment report publicly published for this indication?
□ Yes □ No □ Not applicable

4) Anticipation of the companion test? □ Yes □ No
5) If an assessment of impact for this indication was performed by your organization, could you please rate your evaluation between 1 and 10 (10 being the best: very good anticipation of impact of this new indication, and 1 the lower: many challenges did not enabled us to correctly anticipate the impact of this indication).

□ 1 □ 2 □ 3 □ 4 □ 5 □ 6 □ 7 □ 8 □ 9 □ 10

6) Please indicate the eventual challenges encountered for the assessment of impact of this new indication:

_____
_____
_____

Pembrolizumab (Keytruda) as monotherapy for the first-line treatment of metastatic non-small cell lung carcinoma (NSCLC) in adults whose tumours express PD-L1 with a ≥50% tumour proportion score (TPS) with no EGFR or ALK positive tumour mutations.

1) Identification via Horizon Scanning: □ Yes □ No
2) Reason for no identification via Horizon Scanning if applicable:

_____

_____

_____

3) Was an assessment report publicly published for this indication?
□ Yes □ No □ Not applicable

4) Anticipation of the companion test? □ Yes □ No
5) If an assessment of impact for this indication was performed by your organization, could you please rate your evaluation between 1 and 10 (10 being the best: very good anticipation of impact of this new indication, and 1 the lower: many challenges did not enabled us to correctly anticipate the impact of this indication).

□ 1 □ 2 □ 3 □ 4 □ 5 □ 6 □ 7 □ 8 □ 9 □ 10

6) Please indicate the eventual challenges encountered for the assessment of impact of this new indication:

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_____

_____

Durvalumab (Imfinzi) as monotherapy is indicated for the treatment of locally advanced, unresectable non-small cell lung cancer (NSCLC) in adults whose tumours express PD-L1 on ≥ 1% of tumour cells and whose disease has not progressed following platinum-based chemoradiation therapy.

1) Identification via Horizon Scanning: □ Yes □ No
2) Reason for no identification via Horizon Scanning if applicable:

_____

_____

_____

3) Was an assessment report publicly published for this indication?
□ Yes □ No □ Not applicable

4) Anticipation of the companion test? □ Yes □ No
5) If an assessment of impact for this indication was performed by your organization, could you please rate your evaluation between 1 and 10 (10 being the best: very good anticipation of

impact of this new indication, and 1 the lower: many challenges did not enabled us to correctly anticipate the impact of this indication).

□ 1 □ 2 □ 3 □ 4 □ 5 □ 6 □ 7 □ 8 □ 9 □ 10

6) Please indicate the eventual challenges encountered for the assessment of impact of this new indication:

_____
_____
_____

Tecentriq (atezolizumab) as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma (UC): - after prior platinum-containing chemotherapy, or -who are considered cisplatin ineligible, and whose tumours have a PD-L1 expression ≥ 5%

1) Identification via Horizon Scanning: □ Yes □ No
2) Reason for no identification via Horizon Scanning if applicable:

_____
_____
_____

3) Was an assessment report publicly published for this indication?
□ Yes □ No □ Not applicable

4) Anticipation of the companion test? □ Yes □ No
5) If an assessment of impact for this indication was performed by your organization, could you please rate your evaluation between 1 and 10 (10 being the best: very good anticipation of impact of this new indication, and 1 the lower: many challenges did not enabled us to correctly anticipate the impact of this indication).

□ 1 □ 2 □ 3 □ 4 □ 5 □ 6 □ 7 □ 8 □ 9 □ 10

6) Please indicate the eventual challenges encountered for the assessment of impact of this new indication:

_____
_____
_____

Other open questions

Do you think that having a Horizon scanning system enable a faster access to innovative therapies?

□ Yes □ No

Comment:

_____

_____