iPAAC
INNOVATIVE PARTNERSHIP
FOR ACTION AGAINST CANCER

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Reference frameworks linked with the access to innovative therapies

Restriction of uses, condition of reimbursement and early access programs for unapproved indications – WP9 task 1

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Abbreviations

ALL	Acute lymphoblastic leukemia
ASCO	American Society of Clinical Oncology
CAR-T	Chimeric Antigen Receptor-T
CHAFEA	Consumers, Health, Agriculture and Food Executive Agency
CPG	Clinical Practice Guidelines
EAU	European Association of Urology
ECPC	European Cancer Patient Coalition
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicine Agency
ESMO	European Society of Medical Oncology
EU	European Union
EUnetHTA	European Network for Health Technology Assessment
FDA	Food and Drug Administration
GoR	Grade of Recommendation
HSCT	Hematopoietic Stem Cell Transplantation
HTA	Health Technology Assessment
INAHTA	International Network of agencies for Health Technology Assessment
INCa	French National Cancer Institute
iPAAC	Innovative Partnership for Action Against Cancer
MA	Marketing Authorization
LoE	Level of Evidence
MSI	Micro Satellite Instability
NCCN	National Comprehensive Cancer Network
NICE	National Institute for Health and Care Excellence
NSCLC	Non-Small Cell Lung Cancer
PS	Performance Status
SEOM	Spanish Society for Medical Oncology
SITC	Society for ImmunoTherapy of Cancer
TNCD	French national thesaurus of digestive oncology
WP	Work Package

Executive summary

Objectives

In the context of the iPAAC European joint action, the WP9, dedicated to innovative therapies in cancer, had conducted a review of reference frameworks related to the use of innovative therapies in cancer. The most recent immunotherapies: checkpoint inhibitors and CAR-T cells were taken as focus. Access, in terms of reimbursement was assessed with a focus on the potential restrictions existing in European countries. The goal was to highlight the main factors leading to restrictions of reimbursement, and thus to limited access in European countries, and to think about ways to overcome and to limit these factors. In addition, the existing early access programs for unapproved indication in Europe were also reviewed.

Method

For this purpose, a survey through questionnaires was conducted. After a preliminary literature review, a first questionnaire was sent to iPAAC partners, including questions related to clinical practice guidelines (see other task 1 deliverable), condition of reimbursements of checkpoint inhibitors and CAR-T cells and early access programs for unapproved indications. A second questionnaire was sent to different stakeholders to better understand their opinion on access to innovative immunotherapies

Results

Reimbursement and access to innovative immunotherapies in Europe

In total, 24 replies were collected for 23 countries (2 from Spain). Most of the countries who participated to the questionnaire have a public fund available to finance innovative immunotherapies. In these countries, there were no out-of-pocket costs for patients. Some countries had no or limited access, whereas on the opposite, 7 countries have high access with over 15 indications out of 22 reimbursed with no restrictions compared to European marketing authorization. The other countries which provided a reply to our questionnaire had moderate access.

In terms of immunotherapies and indications having the best access in terms of reimbursement, it was noted that pembrolizumab as monotherapy for the treatment of advanced melanoma was reimbursed in 90,5% of countries. This was the only indication which had been assessed for reimbursement in all countries/regions. Additionally, nivolumab as second-line monotherapy was reimbursed in 82% of the countries replying to the questionnaire for the treatment of advanced renal cell carcinoma and in 78.3% for the treatment of non-small cell lung cancer. Pembrolizumab, as monotherapy for the first-line treatment of metastatic NSCLC in adults whose tumours express PD-L1 with a TPS ≥ 50% was also reimbursed in 78,3% of the countries.

More controversial results were observed for other indications. For instance, lots of restrictions of reimbursement were observed for nivolumab as monotherapy, or in combination with ipilimumab, for the treatment of advanced melanoma in adults. Indeed, some countries restrict the reimbursement only for BRAF-wild patients, some have defined restrictions if the patients do not present the same criteria than for clinical trials inclusion (e.g. ECOG 0 and 1; no brain metastasis). These discrepancies are in accordance with the heterogeneity observed in clinical pratice guidelines for the management of BRAF mutated patients. Despite the extension of indication of ipilimumab for pediatric patients (12-17 yr old), the access to ipilimumab for this population was very limited.

The access was even more restrictive for indication like urothelial carcinoma. The use of pembrolizumab and nivolumab was not reimbursed for urothelial carcinoma in about 20% and not yet assessed in 30% of the countries repliying. In this regard, several HTA agencies had a négative opinion for this indication (e.g. NICE, SMC Scotland, IQWIG). For Hodgkin lymphoma, it was noted that there was still a third of countries for which the reimbursement of pembrolizumab and of nivolumab was still not assess almost 2 years post EMA approval.

Early access programs

About half of the countries (10/22, 45%) mentioned that they had an existing program enabling early access to innovation therapies against cancer (before marketing authorization or before extension of indication). This includes compassionate use programs with financial support provided by pharmaceutical industries. But some countries have other kind of programs in place with public financing, such as France, Portugal and Germany.

Opinions of stakeholders regarding the access to innovative immunotherapies

The opinion of stakeholders on access to innovative immunotherapies was collected with a second questionnaire. Healthcare professionals, HTA agencies, health & medicines agencies, cancer institutes and patients were consulted. 54 replies were obtained from 20 different countries. 55% of the respondents thought that the system in place in their country/region enabled a proper access to innovative immunotherapies in terms of reimbursement. Strong interactions between the different national and regional agencies seems to be important to enable better access. Clear defined pathways and juridical frameworks seem to facilitate access to innovative therapies in terms of reimbursement.

Regarding early access programs, less than half of the repliers (47%) were able to say that there was such an existing program enabling the access to innovative immunotherapies prior marketing authorization in place in their country. However, the satisfaction regarding implemented programs was high: 80% of the persons who replied that there was a system in place in their country were satisfied with their implemented system.

Early access programs as seen as a good help to bridge the gap between the obtention of marketing approval and definition of the price and the decision for reimbursement. It is also important to have these kind of programs for patients who would have no other alternatives. On the other hand, it was also mentioned that early use should be very restrictive to clearly outstanding drugs. In the case of early access, patients should be clearly informed that they are receiving a drug with no approved marketing authorization.

<u>Discussion and remaining challenges</u>

Three main factors leading to restrictions of reimbursement / access of innovative therapies were identified: the low level of scientific and medical evidence supporting marketing authorization, missing direct comparison data with alternative therapies, and high costs. Possibilities to reduce and limit these factors are provided in the discussions.

Overall, for the implementation of frameworks and programs to enable early access for an unapproved indication of an innovative therapy, two main aspects stood out: the need to have clear defined pathways and frameworks, and the need to have strong discussion among the different stakeholders.

Finally, to reduce inequities in terms of access to innovative immunotherapies, it was highlighted that strenghten collaboration between healthcare system players seem to benefit patients. Several suggestions for control rising prices are also discussed.

Acknowledgment

The iPAAC WP9 acknowledges all its partners including the following organizations: Sciensano, the Catalonia institute of oncology, the clinical center of Kragujevac, the Aviano Oncological reference center, the Vilnius university hospital Santaros Klinikos, the biomedical research center of Slovak academy of sciences, the Italian Istituto Superiore di Sanita, the National Cancer Institute of Luxembourg (INC), the European society for pediatric oncology (SIOPE), the European hospital and healthcare federation (HOPE), the association of European Cancer Leagues (ECL), the European Cancer Patient Coalition (ECPC), the biomedical research center network CIBERONC and the Biomedical Research Institute INCLIVA.

The WP9 also thanks all persons who have contributed to the questionnaires related to this work in addition to our partners including: the Portuguese General direction of health, the Austrian Public Health Institute, the Croatian National Cancer registry, the German Cancer Society, the Bank of Cyprus Oncology Center, the Finnish Cancer Society, the Moldavian institute of oncology, the Czech Institute of Health Information and Statistics, the Health Insurance Institute of Slovenia, the ministries of health from Malta and from the Netherlands, the Irish National Cancer Control Programme, the National Cancer institute of Slovakia, the University of Crete, the Hungarian National Institute of Oncology.

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 will be 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.

The panel of anticancer drugs available has strongly evolved over the past few years. Indeed, the dynamic research has brought many innovative treatment options. The most recent arrival of specific immunotherapies has upset the landscape of cancer drugs. Immunotherapy essentially acts upon the patient's immune system to give it the ability to attack cancer cells. In this field, a major change was seen with the introduction onto the market of checkpoint inhibitors (anti-PD-1, anti-PD-L1, anti-CTLA-4). These drugs help inhibit "immune system brakes" (PD-1, PD-L1, CTLA-4) and as such reactivate the immune system so that it fights tumour cells more effectively.

More recently, the arrival of CAR-T (Chimeric Antigen Receptor-T) cells on the European market was also associated with many challenges. In this type of advanced therapy medicinal products (ATMPs), immune cells - T cells - are extracted from the patient's blood and then genetically modified in a laboratory to express specific receptors on their surface. Specific receptors expressed on the surface of the modified T cells, known as CAR-T cells, enable them to detect antigens present on the surface of the tumour cells and provide co-stimulatory proteins of the immune response.

Both checkpoint inhibitors and CAR-T cells are associated with numerous challenges, particularly in terms of clinical research and identifying responder patients, best practices in terms of therapeutic strategies and safety of use, care organisation and economic factors. This is why the WP9 has decided to focus on these therapies and their associated challenges.

The second objective of the WP9 task 1 was to analyse reference frameworks related to the use of innovative immunotherapies. First of all, restrictions regarding the use of innovative immunotherapies compared to their European marketing authorizations were highlighted. For this purpose, a survey was conducted and reference frameworks from HTA agencies have been analysed. Availability and accessibility to innovative immunotherapies in the European countries in terms of reimbursement were also assessed and inequalities pointed out. Knowing that the reimbursement of these therapies evolves very fast these days, the WP9 did not aim to maintain an updated picture of innovative immunotherapies reimbursement in Europe, but rather to highlight the main factors leading to restrictions of reimbursement in

order to better understand restrictions of access and uses. Suggestions to overcome and to limit these factors are presented in the results and further developed in the discussion part. Finally, the WP9 aimed to characterize existing programs/reference frameworks enabling an early access to innovative immunotherapies for an unauthorized indication.

2 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. Data collected for task 1 are based on a literature review as well as from the analysis of the questionnaire results.

Regarding the scope of the task 1, it was agreed to focus first on the following innovative immunotherapies: checkpoint inhibitors and CAR-T cells. Regarding the reference frameworks, it was agreed to focus on two specific aspects:

1) Restrictions of uses of innovative immunotherapies (limitation of reimbursement, especially based on HTA opinions)
2) Programs/Frameworks enabling early access to innovative immunotherapies for unapproved indications

2.1 Identification of restrictions of innovative immunotherapies uses and reimbursement

2.1.1 Questionnaire addressed to iPAAC partners about innovative immunotherapies reimbursement modalities

The second part of the questionnaire addressed to iPAAC partners was aiming to collect data regarding the availability and accessibility to innovative immunotherapies in European countries. General questions about overall reimbursement modalities were integrated to better understand the structure of reimbursement system in each country.

Then, for each European approved indication of checkpoint inhibitors and CAR-T cells, responders were requested to specify if this indication was:

1) Not reimbursed
2) Reimbursed for the whole indication
3) Partially reimbursed with some restrictions compared to the EMA marketing authorization
4) Not yet assessed

Questions regarding the modalities for reimbursement of companion tests associated with some indication were also integrated, as well as potential restrictions of prescribers.

2.1.2 Review of HTA opinion restricting the use of immunotherapies

Some questions were included in the questionnaire addressed to iPAAC partners about the potential existence of an HTA organizations and aiming to understand if innovative immunotherapies had already been assessed in terms of HTA in these countries.

In addition, websites from health technology agencies and health care agencies were consulted to identify HTA/medico-economic assessment publicly published.

The EUnetHTA network (https://www.eunethta.eu/about-eunethta/eunethtanetwork/) as well as the INAHTA members list (http://www.inahta.org/members/members_list/) were consulted to identify all potential additional European HTA opinions.

For each HTA opinion publicly available on innovative immunotherapies, the following information was collected:

- Country
- Name of the organization who published the HTA opinion
- Molecule assessed
- Therapeutic indication
- Date of the HTA opinion

There were then assessed and categorized whenever possible between 3 main categories:

- Positive opinion
- Negative opinion
- Opinion suggesting restriction of uses

The main restrictions were listed by molecule and by indications. The factors leading to such restrictions were highlighted whenever clearly provided to support the discussion part.

A parallel was then performed to compare whether restrictions identified in HTA opinions were in correlation with restrictions of reimbursement observed.

Due to the fast evolution of reimbursement decision in the field of innovative therapies, the WP9 was not able to maintain up to date information regarding the reimbursement of innovative immunotherapies in Europe. However, it was considered that working on data collected at the end of 2018 would already provide a good overview of the main factors leading to restrictions of reimbursement.

2.2 Frameworks and programs enabling early access to innovative immunotherapies for unapproved indications

2.2.1 Identification of programs with the questionnaire addressed to iPAAC partners about early access programs for unapproved indications

The third part of the questionnaire sent to iPAAC partners included questions related to early access to innovative immunotherapies for unapproved indications. The goals of the questions included were to:

1) Determine where in Europe such programs exist
2) Get a brief description of each program

2.2.2 Presentation of key points of programs enabling early access to innovative immunotherapies for unapproved indications

For each program identified, the following characteristics have been collected when available:

- Name of the program

- Agency/organization in charge of the initiative
- Geographical localization
- Start date of the program
- Brief description of the program
- References for more details

If the details of programs identified through the questionnaire were not sufficient, an additional literature review was performed specifically on this program.

2.3 Collection of stakeholders opinion

A second questionnaire aimed to collect stakeholders' opinions on the following topics:

- Reimbursement of innovative immunotherapies
- Early access for unapproved indications

The goal was to obtain a good understanding on the perception of access (in terms of reimbursement & early access for unlabelled indications) to innovative immunotherapies, and if possible get a better understanding of pros and cons of existing programs for such accesses.

This questionnaire was addressed to:

- HTA agencies
- Health and medicines agencies
- Cancer institutes
- Patient associations

3 Results

The detailed results from the questionnaire addressed to iPAAC partners regarding overall completion are provided within the other deliverable linked to task 1 (See paragraph 3.4.1 - Completion of the questionnaire.)

3.1 Access and restrictions of innovative immunotherapies use

3.1.1 Comparison of access to innovative immunotherapies in terms of reimbursement between European countries

Most of the countries who participated to the questionnaire have a public fund available to finance these innovative immunotherapies, except in Moldova where no fund were available for these therapies. In Lithuania, Norway and Ireland, there is a mix of public and private financing. In countries where there is a public fund available, there are no out-of-pocket costs for patients.

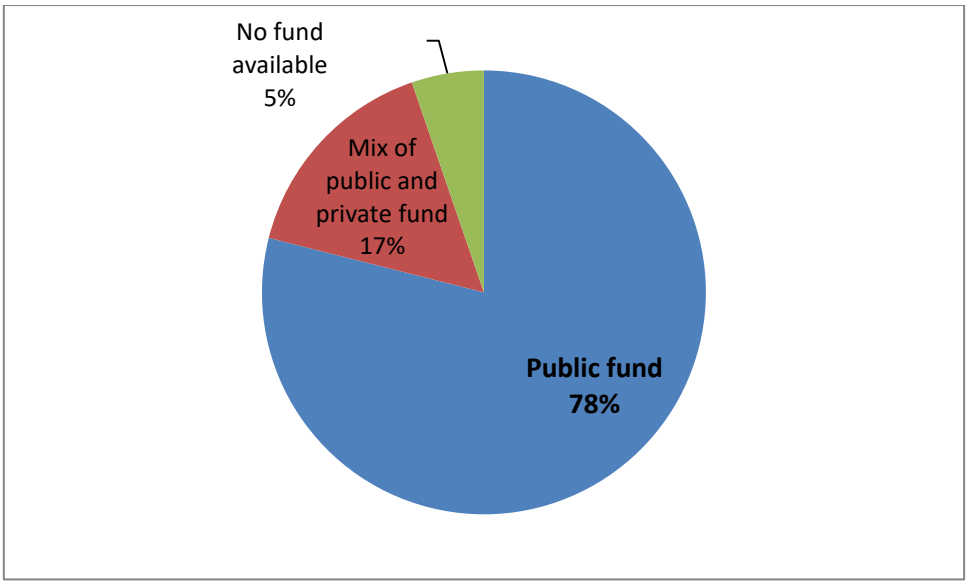


Figure 1: Financing of innovative immunotherapies in European Union

The graph below represents Europe with the classification of countries in 3 categories depending on access to innovative immunotherapies in terms of reimbursement.

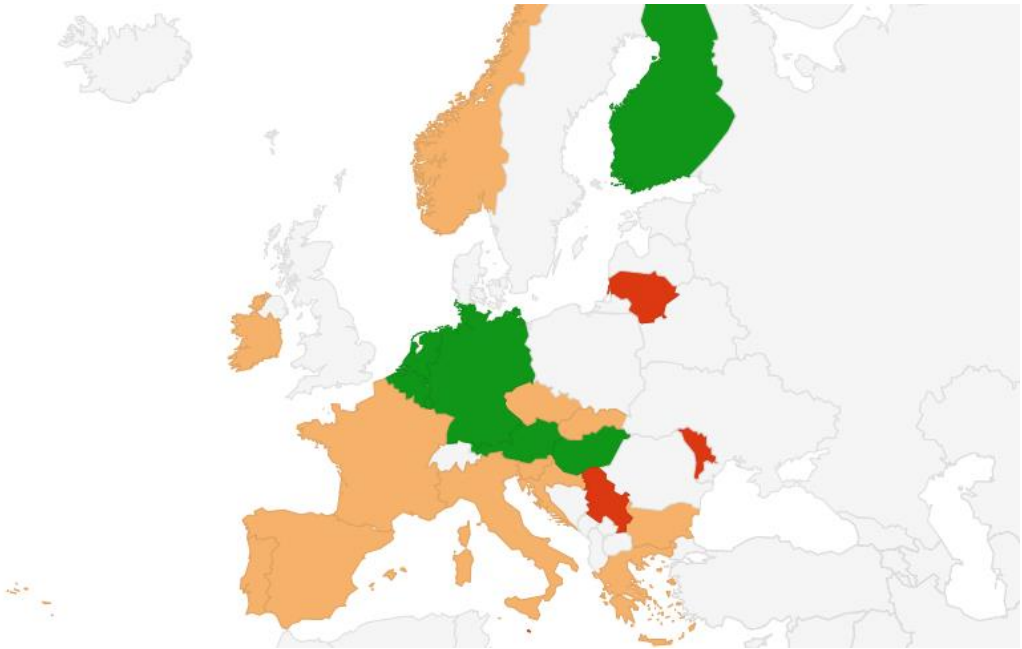


Figure 2: Comparison of access to innovative immunotherapies in European Union – data from Dec 2018*

High access (≥ 15 indications reimbursed with no restrictions compared to EU MA)

Moderate access

No access or very limited

*To be noted that additional data were provided for the countries with limited access and are described below

Overall, 4 countries had no access to innovative immunotherapies (or very limited) at the time of the questionnaire completion:

- 2 countries did not have access to any innovative immunotherapies in terms of reimbursement for all types of cancer: Malta and Moldova. The responder for Malta specified that when they checked the answer 'Not reimbursed', it meant, in the context in Malta, that the drug was approved but not reimbursed, because not yet available through the free medicines program of the government.
- Additional data were provided for Malta in February 2020:
    - In May 2019, nivolumab was introduced on the Government Formulary List for inpatient use. Nivolumab 10mg/mL concentrate for solution for infusion can be prescribed by Consultant Oncologists and Consultant Haematologists. Nivolumab had been made available for patients with: Melanoma, Adjuvant treatment of Melanoma, Non-Small Cell Lung Cancer, Renal Cell Carcinoma, classical Hodgkin lymphoma, Squamous Cell Cancer of the Head and Neck and Urothelial Carcinoma.
    - Pembrolizumab is currently at the final procurement stages
- For Lithuania, only the indications for lung cancer were assessed, but none of them were reimbursed at the time of questionnaire and according to the obtained answers. However, during the review of this report, our partner underlined several key points. Nivolumab and atezolizumab have been reimbursed for non small cell lung cancer. For melanoma, pembrolizumab and nivolumab are available since Q2 2018. These drugs must be prescribed with restrictions compared with full authorised registration. Moreover, ramucirumab will probably be reimbursed at the end of the year ;
- In Serbia, only one immunotherapy was reimbursed at the time of the questionnaire: pembrolizumab for its indication in melanoma. The decision for the reimbursement of nivolumab was expected in the coming months.

Seven countries had a high access to innovative immunotherapies as at least 15 out of the 22 indications assessed in the questionnaire were reimbursed with no restrictions compared to the approved European marketing authorization: Netherlands, Finland, Germany, Luxembourg, Belgium Austria and Hungary.

In the 12 remaining countries, the access was judged moderate. For France, the assessment of reimbursement availability was performed based on the inscription on the “liste en sus”, so this did not include other possible financing method for innovative therapies such as ATU/post ATU systems.

In Norway, it was specified that the reimbursement was possible with restrictions compared to the EU marketing authorizations thanks to the “preapproved application to Norwegian Health Economics Administration (HELFO)”.

For Slovakia, Croatia, Czech Republic, almost all indications were reimbursed with restrictions compared to EU marketing authorization but no details were provided.

The immunotherapies and indications for which there was the best access were:

1) Pembrolizumab as monotherapy for the treatment of advanced melanoma:
reimbursed in 90,5% of the countries, including 67% with no restrictions compared to the European markerking authorization, and assessed in all countries.

2) Nivolumab as second-line monotherapy for the treatment of advanced renal cell carcinoma: reimbursed in 82% of the countries including 59,1% with no restrictions compared to European markerking authorization
3) Nivolumab as monotherapy for the treatment of NSCLC as second line (after chemotherapy): reimbursed in 78,3% of the countries including 61% with no restrictions compared to the European markerking authorization
4) Pembrolizumab as monotherapy for the first-line treatment of metastatic NSCLC in adults whose tumours express PD-L1 with a TPS ≥ 50%: reimbursed in 78,3% of the countries/regions including 61% with no restrictions compared to the European markerking authorization

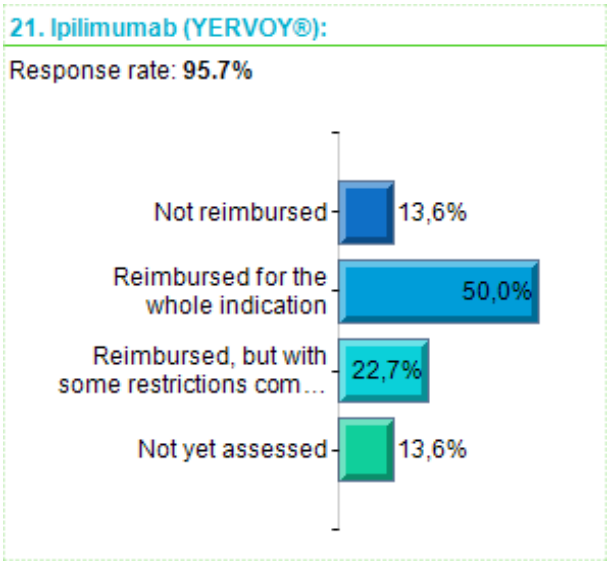
3.1.2 Detail of reimbursement of innovative immunotherapies per indications

For each of the following European approved therapeutic indications, responders were requested to indicate if these drugs were reimbursed in their country. If there was some restrictions in terms of reimbursement compared to the European marketing authorizations, responders were requested to specify the type of restrictions. The results are presented by cancer types.

Melanoma

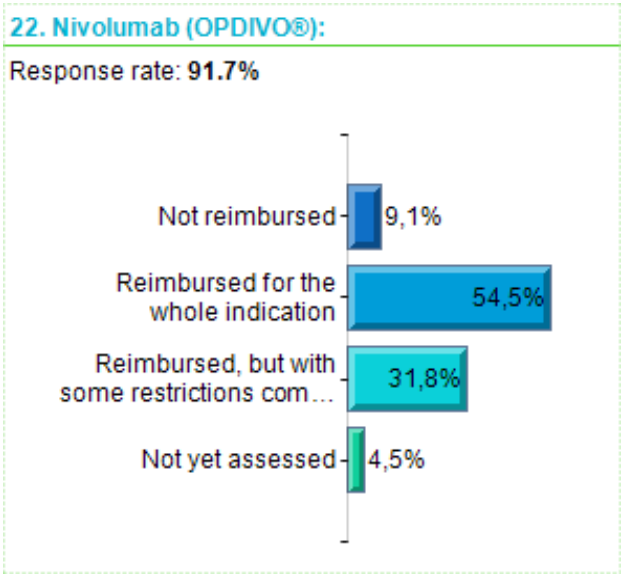
- Ipilimumab (YERVOY®):

YERVOY as monotherapy is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults, and adolescents 12 years of age and older.

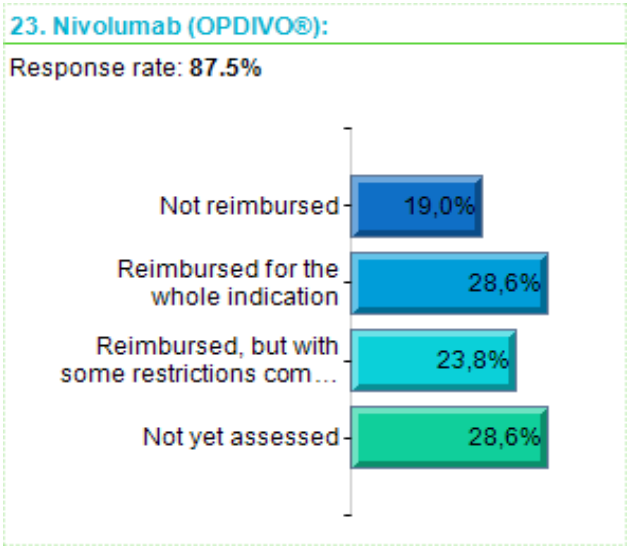


- Nivolumab (OPDIVO®):

OPDIVO as monotherapy or in combination with ipilimumab is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults.

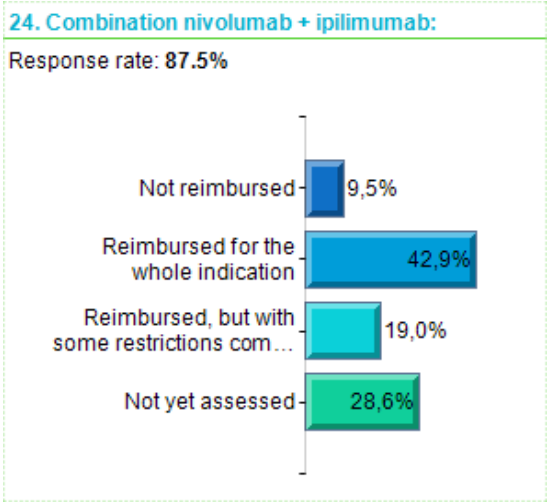


OPDIVO as monotherapy is indicated for the adjuvant treatment of adults with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection.



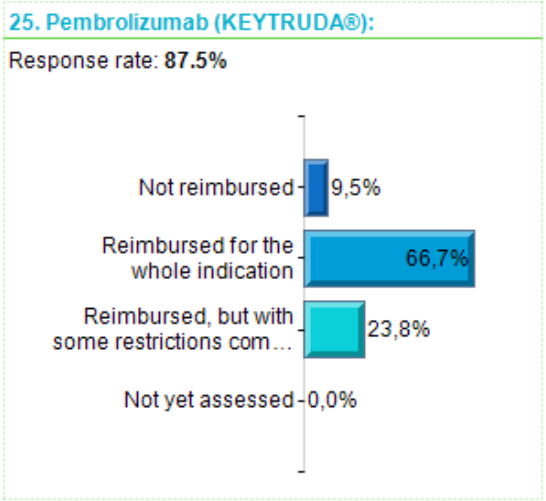
- Combination nivolumab + ipilimumab:

YERVOY in combination with nivolumab is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults.



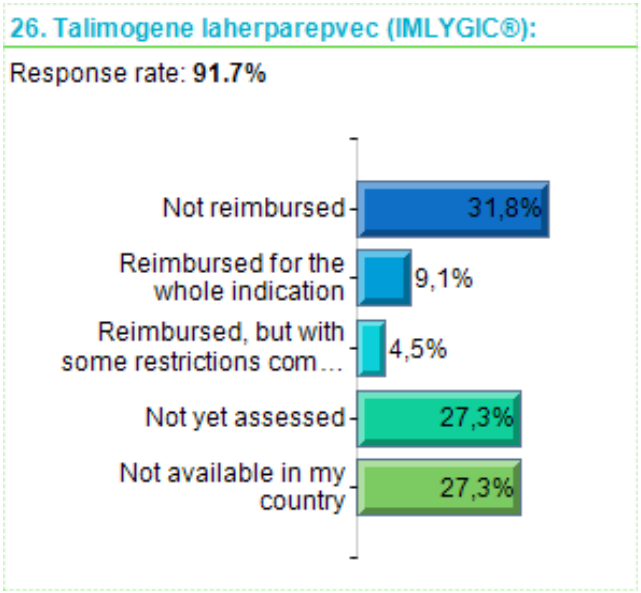
- Pembrolizumab (KEYTRUDA®):

Keytruda as monotherapy is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults.



- Talimogene laherparepvec (IMLYGIC®):

Imlygic is indicated for the treatment of adults with unresectable melanoma that is regionally or distantly metastatic (Stage IIIB, IIIC and IVM1a) with no bone, brain, lung or other visceral disease.



Comments obtained from the questionnaire regarding restriction for melanoma:

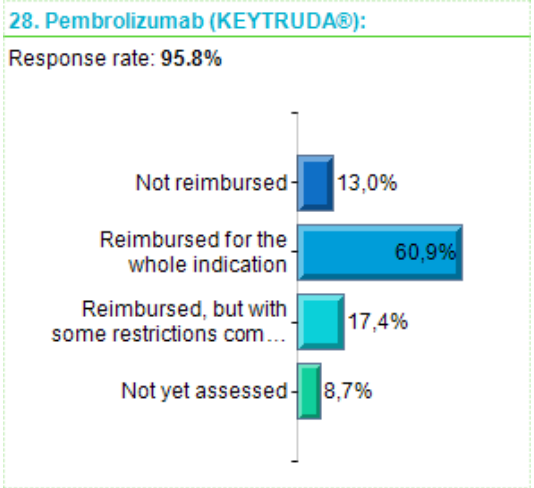
- Belgium: Yervoy monotherapy: **patient must be at least 18 years and have ECOG 0 or 1**
- Spain: Reimbursement conditions depend on the region. R**estrictions related to trial results** were noted in Catalonia.
- France: The assessment was performed considering that these drugs were reimbursed for an indication when they were registered on the "liste en sus" for this specific indication. The registration on the "Liste en sus" enables a specific financing modality to access to innovative and highly expensive drugs. As Yervoy is not registered on this list, the access to this medicine is limited. This explains why there are some restrictions concerning the reimbursement of the association nivolumab + ipilimumab.
- Cyprus: Nivolumab is reimbursed only in metastatic melanoma and not adjuvant
- Serbia: Reimbursement of pembrolizumab for the treatment of unresectable or metastatic melanoma in adults, with **BRAF negative mutation, as monoterapy, for patients with EC0G PS 0-1**. (only pembrolizumab is reimbursed)
- Norway: All indications are reimbursed, but with some restrictions compared to the EMA indication. Comment: Preapproved application to Norwegian Health Economics Administration (HELFO)
- Portugal: Nivolumab is reimbursed, but with some restrictions compared to the EMA indication for the treatment of advanced (unresectable or metastatic) melanoma in adults. Comment: **Without mutations of BRAF, ECOG 0 and 1, no active brain metastasis**
- Czech republic: there are some special restriction specific for each indication

Talimogene was reimbursed only in 4 European countries including one with restrictions compared to the marketing authorization (restrictions were not specified).

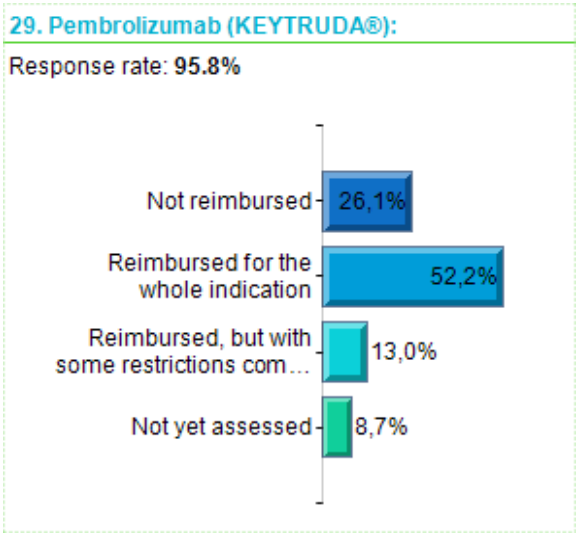
Non-small cell lung cancer

- Pembrolizumab (KEYTRUDA®):

Keytruda as monotherapy is indicated 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.

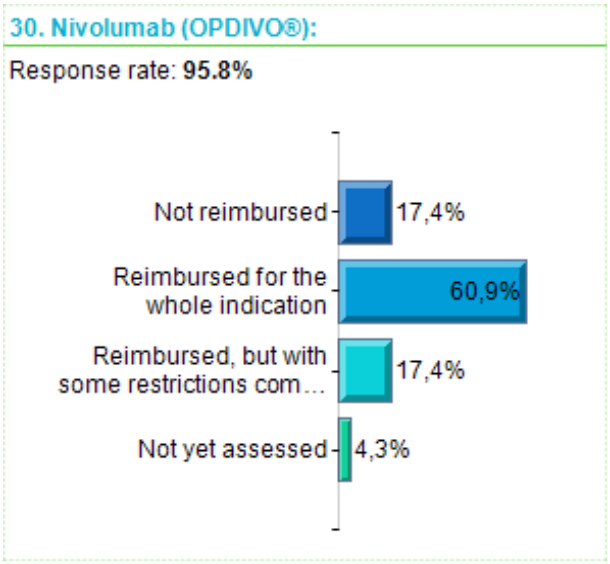


Keytruda as monotherapy is indicated for the treatment of locally advanced or metastatic NSCLC in adults whose tumours express PD-L1 with a ≥1% TPS and who have received at least one prior chemotherapy regimen. Patients with EGFR or ALK positive tumour mutations should also have received targeted therapy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



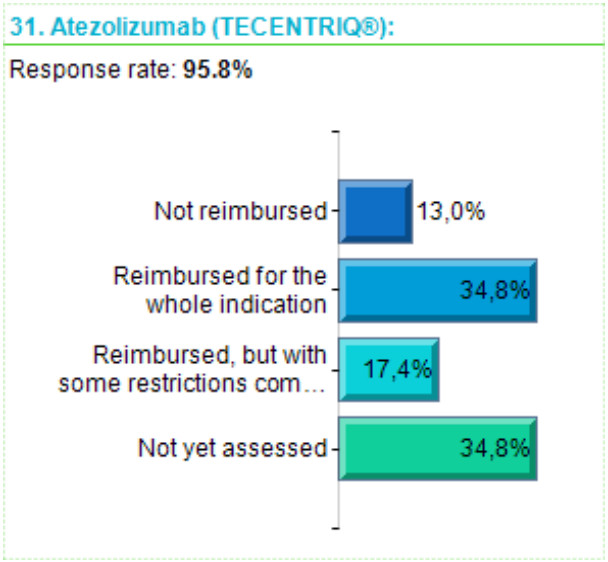
- Nivolumab (OPDIVO®):

OPDIVO as monotherapy is indicated for the treatment of locally advanced or metastatic non-small cell lung cancer after prior chemotherapy in adults.



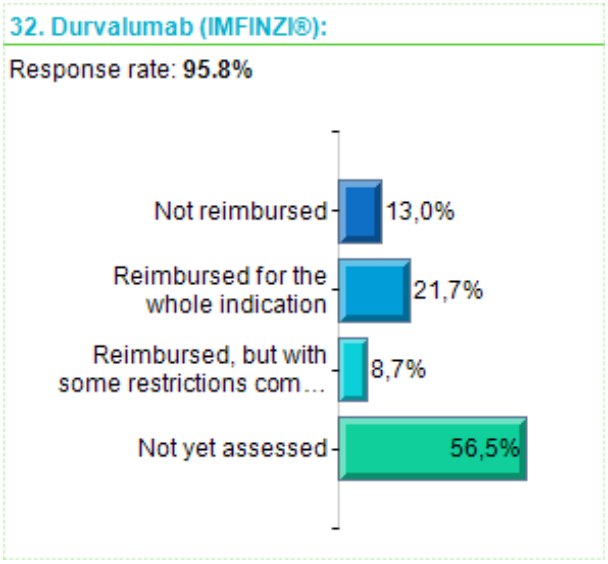
- Atezolizumab (TECENTRIQ®):

Tecentriq as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after prior chemotherapy. Patients with EGFR activating mutations or ALK-positive tumour mutations should also have received targeted therapy before receiving Tecentriq.



- Durvalumab (IMFINZI®):

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.



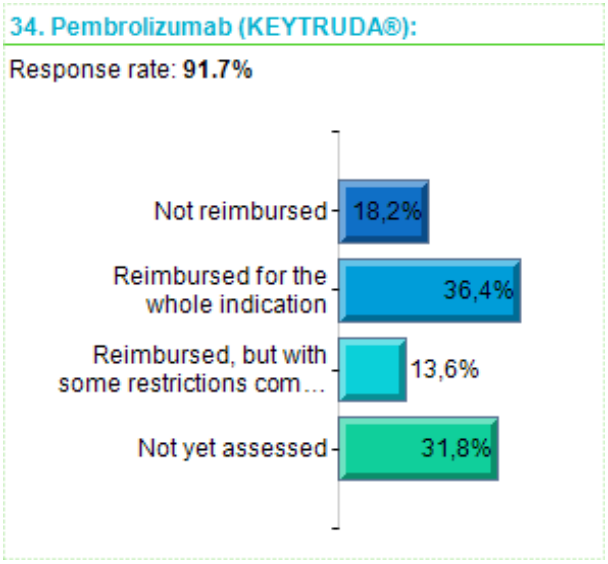
Comments obtained from the questionnaire regarding restrictions for non-small cell lung cancer:

- Belgium: Imfinzi: assessment on going
- Norway: Preapproved application to Norwegian Health Economics Administration (HELFO)
- Czech republic: there are some special restriction specific for each indication

Urothelial carcinoma

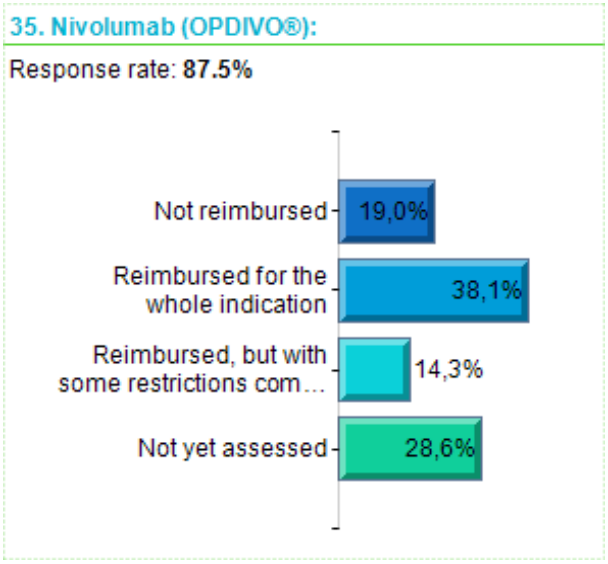
- Pembrolizumab (KEYTRUDA®):

KEYTRUDA as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who have received prior platinum-containing chemotherapy or in adults who are not eligible for cisplatin-containing chemotherapy.



- Nivolumab (OPDIVO®):

OPDIVO as monotherapy is indicated for the treatment of locally advanced unresectable or metastatic urothelial carcinoma in adults after failure of prior platinum-containing therapy.

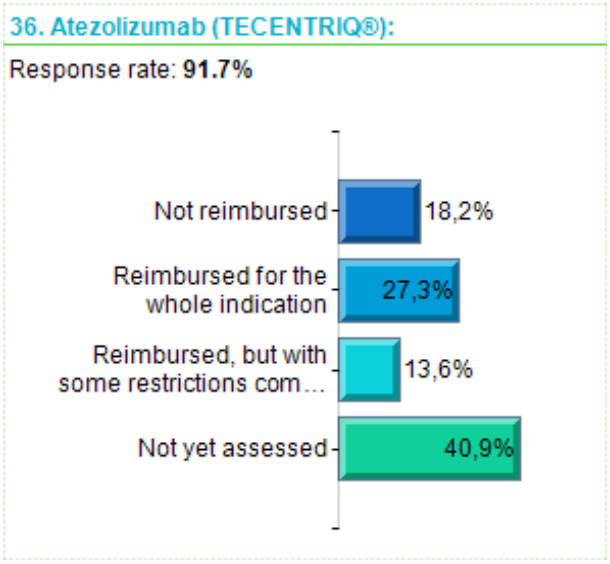


- Atezolizumab (TECENTRIQ®):

Tecentriq 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%



Comments obtained from the questionnaire regarding restrictions for urothelial carcinoma:

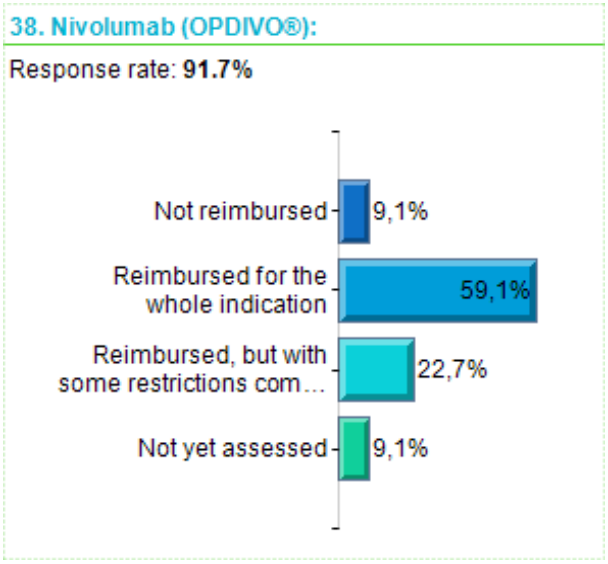
- Norway: Preapproved application to Norwegian Health Economics Administration (HELFO)

For this indication, nivolumab was approved in June 2017 and pembrolizumab in August 2017. There are still about a third of the countries which did not assess these 2 indications, respectively 17 months and 14 months after marketing authorization.

Advanced renal cell carcinoma

- Nivolumab (OPDIVO®):

OPDIVO as monotherapy is indicated for the treatment of advanced renal cell carcinoma after prior therapy in adults.



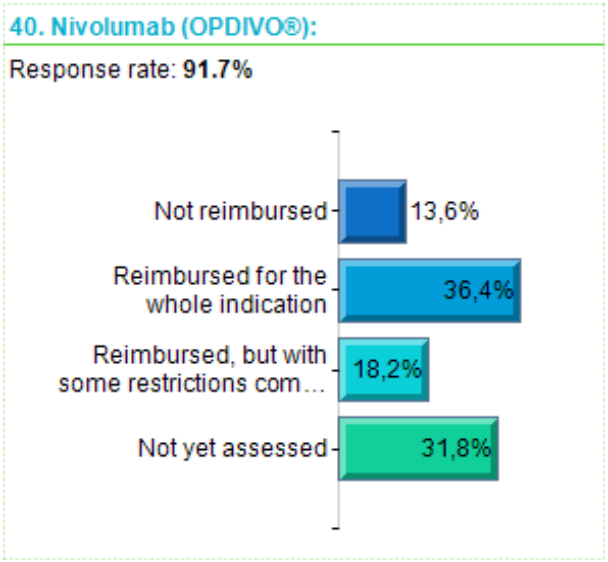
Comments obtained from the questionnaire regarding restrictions for renal cell carcinoma:

- Norway: Preapproved application to Norwegian Health Economics Administration (HELFO)
- Czech republic: there are some special restriction

Progressing squamous cell cancer of the head and neck

- Nivolumab (OPDIVO®):

OPDIVO as monotherapy is indicated for the treatment of recurrent or metastatic squamous cell cancer of the head and neck in adults progressing on or after platinum-based therapy.



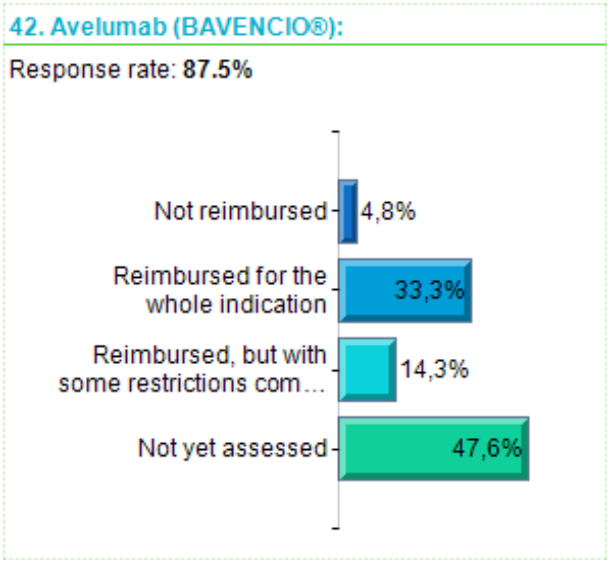
Comments obtained from the questionnaire regarding restrictions for head and neck cancer:

- Norway: Preapproved application to Norwegian Health Economics Administration (HELFO)

Metastatic Merkel cell carcinoma

- Avelumab (BAVENCIO®):

Bavencio is indicated as monotherapy for the treatment of adult patients with metastatic Merkel cell carcinoma.



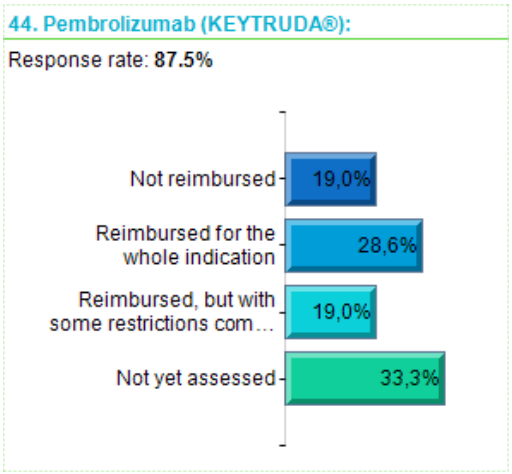
Comments obtained from the questionnaire regarding restrictions for Merkel cell carcinoma:

- Norway: Preapproved application to Norwegian Health Economics Administration (HELFO)

Relapsed or refractory classical Hodgkin lymphoma

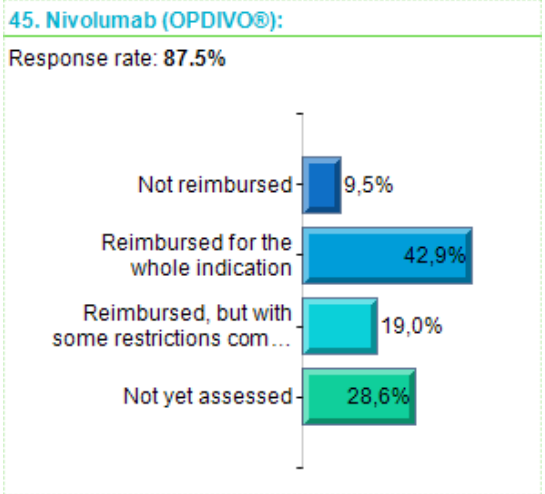
- Pembrolizumab (KEYTRUDA®):

Keytruda as monotherapy is indicated for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma (cHL) who have failed autologous stem cell transplant (ASCT) and brentuximab vedotin (BV), or who are transplant-ineligible and have failed BV.



- Nivolumab (OPDIVO®):

OPDIVO as monotherapy is indicated for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma after autologous stem cell transplant (ASCT) and treatment with brentuximab vedotin.



Comments obtained from the questionnaire regarding restrictions for Hodgkin lymphoma:

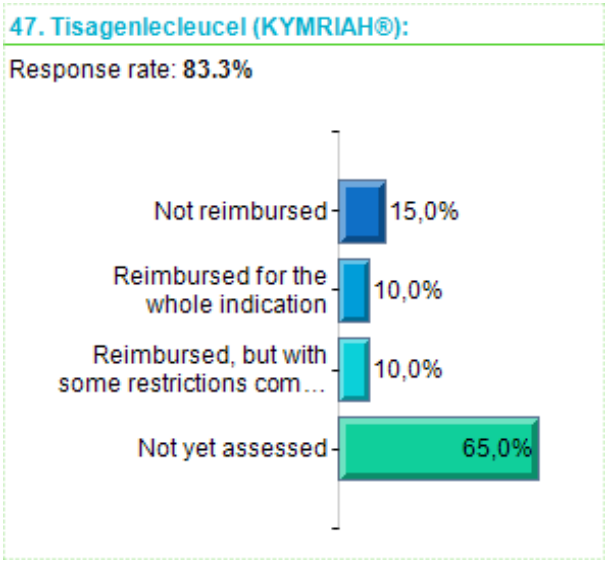
- Ireland: Pembrolizumab is reimbursed with some restrictions: “Pembrolizumab (KEYTRUDA®): is not reimbursed for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma (cHL) who have failed autologous stem cell transplant (ASCT) and brentuximab vedotin (BV)”
- Czech Republic: There is temporary reimbursement (for nivolumab). Pembrolizumab has not been assessed yet
- Norway: Preapproved application to Norwegian Health Economics Administration (HELFO)

For the indication of pembrolizumab for the treatment of relapsed or refractory classical Hodgkin lymphoma, there are still a third of countries which did not take decision on reimbursement a year and a half after EU MA. However, there are about 20% of the countries which took a negative decision for the reimbursement of this therapy.

Refractory B-cell acute lymphoblastic leukaemia:

- Tisagenlecleucel (KYMRIAH®):

KYMRIAH is 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.



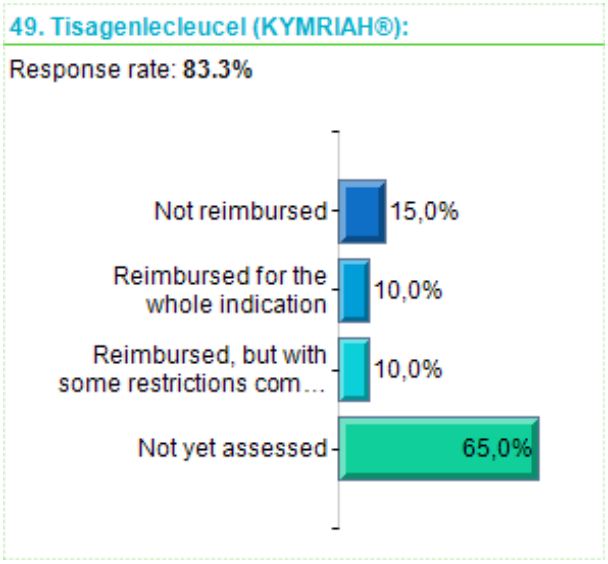
Comments obtained from the questionnaire regarding restrictions for refractory B-cell acute lymphoblastic leukaemia:

- Belgium: Kymriah: assessment on going
- Norway: Kymriah is approved, but not marketed

Large B-cell lymphoma

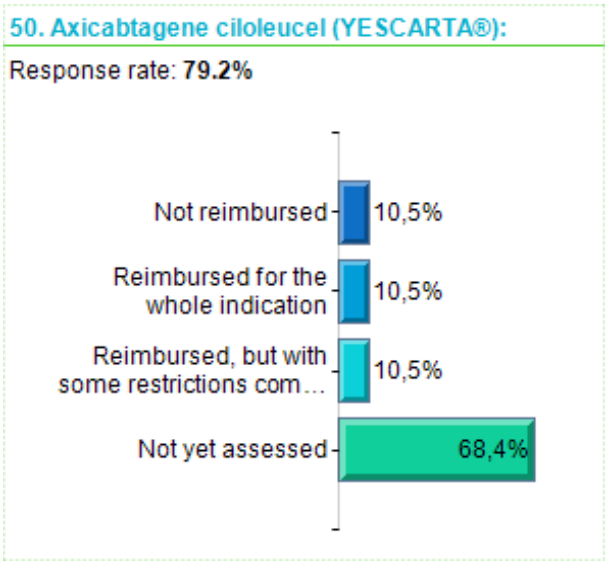
- Tisagenlecleucel (KYMRIAH®):

KYMRIAH is 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®):

YESCARTA is 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.



Comments obtained from the questionnaire regarding restrictions for large B-cell lymphoma:

- Belgium: Kymriah and Yescarta: assessment on going
- Norway: approved, but not marketed

3.1.3 Reimbursement of molecular test associated with innovative therapies

Reimbursement modalities of the molecular test to assess the biomarker when prescriptions of immunotherapies are conditioned by the prerequisite of a specific biomarker expression are presented on the figure below.

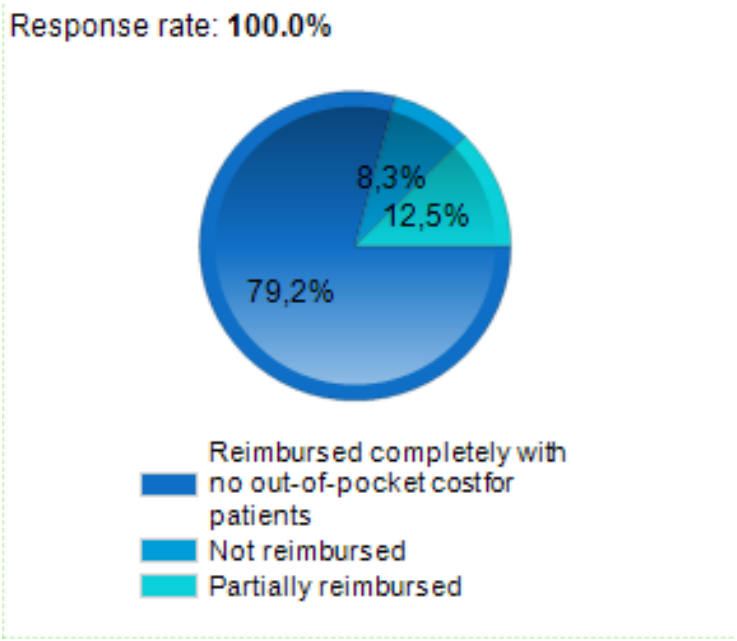
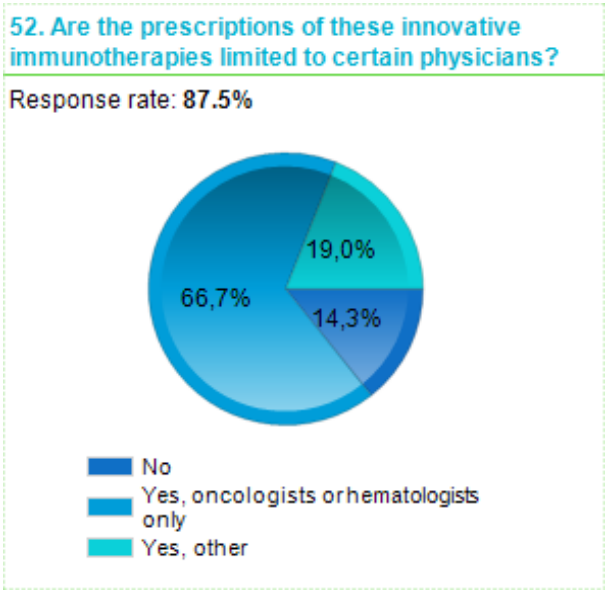


Figure 3: Reimbursement modalities of the molecular test to assess the biomarker when prescriptions of immunotherapies are conditioned by the prerequisite of a specific biomarker expression

Comments provided regarding the financing modalities:

- Belgium: 8 € out of pocket cost for patient; rest is for health insurance
- Spain: depends of the region. In Catalonia: “usually associated to the price of the drug. It is then paid by the industry in specific hospitals, which are used as reference hospitals for this test”
- France: Financed by the ministry of health (RIHN - specific financing for innovative acts)
- Germany: fully reimbursed, if necessary for drug therapy
- Ireland: not reimbursed but funded in the public health system
- Czech Republic: available in Czech at State Institute for Drug Control web
- Malta: the number of tests for specific biomarker expression are sent, accepted and consequently fully reimbursed is limited because these investigations need to be conducted in a foreign laboratory (to date the required expertise and technological capacity are not available in Malta).

3.1.4 Restrictions concerning the prescribers of such innovative immunotherapies



Comments provided in the questionnaire:

- Belgium: oncologist or hematologist or specialized in indication
- Austria: oncologist or specialist in the certain field (dermatologist, surgeon, etc)
- Norway: Treating doctors
- Czech Republic: oncologists or hematologists at special centers only
- Lithuania (feedback obtained during the review of this report) : oncologists and hematologists usually after multidisciplinary treatment decision.

3.1.5 Results from the review of HTA opinions

Overall results

According to the questionnaire replies, about 30% of the responders declared that they had no HTA agency in their countries, including Greece, Hungary, Cyprus, Moldova, and Slovenia. The number of European countries where HTA organizations had been released opinions is displayed on the graph below by innovative immunotherapy (based on questionnaire results).

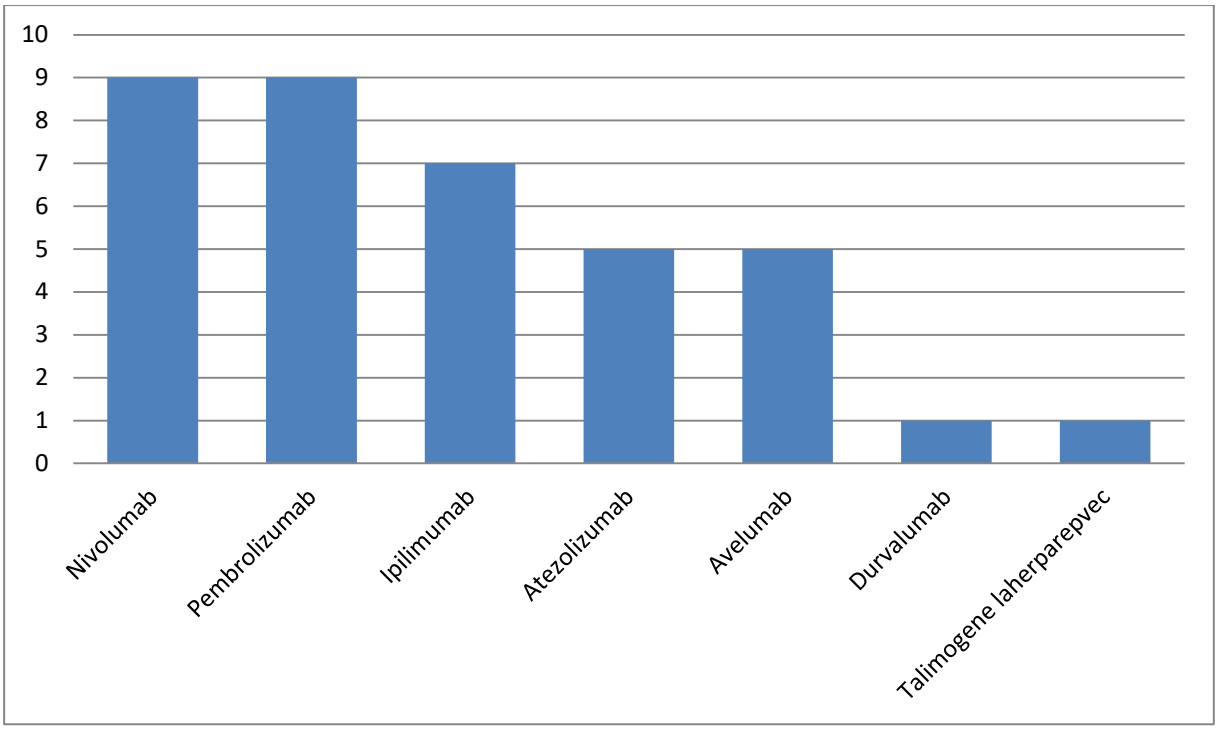


Figure 4: Number of European countries where HTA agencies have released opinions by innovative immunotherapy (Dec 2018)

Additionally, websites from EUnetHTA and INAHTA members were screened, enabling us to identify a total of 14 different agencies who had already published at least one opinion on innovative immunotherapies, at the time of the screening (December 2018), The list of these agencies is provided below.

Table 1: HTA agencies who had already published at least one opinion on innovative immunotherapie (as of December 2018)

Country	HTA Agency	Website
France	HAS	http://www.has-sante.fr/
Ireland	NCPE	http://www.ncpe.ie
UK	NICE	http://www.nice.org.uk/
Finland	FIMEA	http://www.fimea.fi
Germany	IQWIG	http://www.iqwig.de/
Germany	G-BA	http://www.g-ba.de/

Lithuania	State Medicines Control Agency	https://www.vvkt.lt/
Norway	NIPH	http://www.fhi.no/
Poland	AOTMiT	http://www.aotmit.gov.pl
Spain	AETSA	http://www.aetsa.org/
Spain	AQuAS	http://aquas.gencat.cat/ca/inici/
Spain	OSTEBA	https://www.osakidetza.euskadi.eus/informacion/evaluacion-de-nuevos-medicamentos-en-el-ambito-hospitalario/r85-pkcevi03/es/
Sweden	TLV	www.tlv.se
UK - Wales	ATW / AWMSG	http://www.awmsg.org/
UK - Scotland	HIS / SMC	https://www.scottishmedicines.org.uk/home

Some general comments on HTA reports:

- In Malta, the Directorate for Pharmaceutical Affairs within the Ministry for Health is responsible for preparing HTAs. These HTAs are utilized internally as part of the decision making process, including the two advisory committees (Government Formulary List Advisory Committee and the Advisory Committee for Healthcare Benefits). Recommendations are not made publicly available; however a positive recommendation results in public procurement procedures and the inclusion of the recommended medicine on the Government Formulary List (GFL). The GFL is also publicly available.
- Most of the HTA opinions are published in national language, making it hard for the WP9 to assess the content. Some of them provide an English summary such as G-BA in Germany or FIMEA in Finland.
- Lots of variations were noted across the different HTA reports found. The areas covered on HTA reports vary among agencies. Some agencies have one report per medicine and per indication, whereas other have a more global review by therapeutic field such as the Norwegian report reviewing all new drugs for inoperable or metastatic malignant melanoma patients.
- Some HTA agencies publish clear recommendations whereas other publish more neutral assessment reports.
- The methodology for HTA differs also between countries: some countries are performing a review mainly based on cost-effectiveness; other are taking into account clinical information more deeply.

- Time between granting of the marketing authorization and HTA report release varies also a lot (cf: ESMO publication)
- Decision to reimburse or not in not always in accordance with recommendations from HTA reports.
- Scotland, Wales and Poland did not participate in the questionnaire but HTA opinion were found and analyzed.
- In Spain: several HTA agencies exist, at the regional level such as AETSA, AQuAS, and OSTEBA. However, it seems that some regions do not have such HTA organization in place and there is no national in place.
- Some reports compared several immunotherapies versus one another. For example this is the case for TLV in Sweden. They compared Opdivo and Keytruda both for non-small cell lung cancer and melanoma. However, due to missing clinical data; it is not possible to conclude of one product versus another.
- In Lithuania, the HTA reports are publicly available in the website of MoH (currently) and they will be later on published in the website of SMCA. The reports are in Lithuanian.

Most common restrictions of uses observed: Focus on some indications

The HTA opinions publicly available on innovative immunotherapies have been reviewed and categorized. An overview of these opinions content is presented in the appendix 1 by cancer types. The positive opinions are represented in green, the negative ones in red, and restrictions are identified in orange and presented in the second table in the appendix. Other situations are specified directly in the table (e.g. recommendation for reduction of price, neutral assessment …).

At the time of the identification of HTA reports, there was nothing published yet on CAR-T cells. The focus is here made on checkpoint inhibitors.

Overall, the main factors leading to restrictions of uses of innovative immunotherapies observed were:

- Limited efficacy and safety data in the population assessed
- No direct comparison data with other innovative therapies for similar indication/other existing therapeutic alternative
- High costs of these therapies

We will present here a focus on the most recurrent and the most restrictive restrictions observed, by cancer types, to provide examples for the 3 main factors previously pointed out.

<u>Melanoma</u>

- Several HTA agencies such as HAS and IQWIG did not recommend ipilimumab for its extension of indication in pediatric population (12 to 17 years old).
    - In France, an unfavorable opinion to reimburse this indication was published from HAS due to limited efficacy and safety data, superiority of anti-PD-1 compared to ipilimumab in treatment-naïve patients and lack of space in the therapeutic strategy of advanced melanoma in adolescents. This molecule is currently no longer included on the list of products which are reimbursed (“liste en sus”).

  - In Germany, the conclusion of the reevaluation from the IQWIG for the extension of indication brought the conclusion that the additional benefit was not proven for this indication. It is however currently reimbursed in Germany.
- Most of the HTA opinions published for the association nivolumab + ipilimumab included restrictions or at least strong reserve in their conclusions. For instance:
  - In Ireland, this association was considered not cost-effective for the treatment of advanced (unresectable or metastatic) melanoma NCPE assessment and therefore not recommended for reimbursement at the submitted price.
  - Reimbursement was possible as of January 2019.
  - In Finland, FIMEA provided the following conclusion: “In the light of published research data, the efficacy of combination therapy compared to nivolumab monotherapy appears modest in relation to the cost of treatment and its safety profile. Combination thera-py should be considered with reservation until more research data is available on the effect of the treatment on overall survival.” Reimbursement is possible in Finland for this association
- Several restrictions based on the BRAF status were also identified for nivolumab (both in monotherapy and in association with ipilimumab), and pembrolizumab. In this situation, this is also linked with the fact that there is another innovative therapeutic option for the subpopulation of patients with BRAF-mutated tumors (anti-BRAF/anti-MEK). The place in the therapeutic strategy is more difficult to assess between the different innovative therapies as there are no direct data comparing these innovative therapies. This was also observed as one of the main challenges for defining the best therapeutic place in clinical practice guidelines. Some examples:
  - In France, the HAS recommended the association nivolumab + ipilimumab only for ECOG 0 and 1 for patient with B-RAF non mutated tumors and no cerebral metastasis by HAS.
  - In Germany, IQWIG recommended the association nivolumab + ipilimumab only for BRAF wild tumors who did not receive prior treatment only. No clinical advantages were foreseen for BRAF mutated tumors. Similarly, no added benefit was seen by IQWIG for the treatment of non-pre-treated patient with BRAF-mutated tumors with pembrolizumab.
  - In Spain, AQuAS considered that the treatment with pembrolizumab in advanced melanoma was not adequate for patients presenting BRAF V600 mutated with signs and symptoms that suggest a rapid evolution of the disease as long as they have not received a BRAF / MEK inhibitor previously.
- Other recommendations for restrictions of uses and/or reserve in opinions were observed based on the clinical trial exclusion criteria such as:
  - the functional status (e.g. restrictions made by AQuAS for pembrolizumab and nivolumab: patients should have ECOG 0-1);
  - patient’s expectation of survival (e.g. restrictions made by AETSA for ipilimumab: patient’s expectation of survival should not be inferior at 4 months);
  - Cerebral metastasis (restrictions made by AQuAS for ipilimumab for patients presenting symptomatic or asymptomatic central nervous metastases that require treatment with corticosteroids);
  - no previous treatment received (e.g. nivolumab in combination with ipilimumab for the treatment of advanced (unresectable or metastatic) melanoma in adults had been accepted for restricted use within NHS Scotland

with the SMC restriction for the first-line treatment of advanced melanoma only.

Lung cancer

- Restrictions for patients with advanced NSCLC with ALK rearrangement:
  - In France, HAS did not recommend the reimbursement of atezolizumab for advanced NSCLC with ALK rearrangement. However, no restrictions have been implemented for this population on this parameter for the reimbursement conditions.
- Restrictions concerning PD-L1 expression:
  - In UK, the NICE recommended nivolumab for use within the Cancer Drugs Fund as an option for treating locally advanced or metastatic **non-squamous** non-small-cell lung cancer in adults after chemotherapy, **only if their tumours are PD-L1 positive** (and nivolumab is stopped at 2 years of uninterrupted treatment, or earlier in the event of disease progression, and the conditions in the managed access agreement are followed).
  - In Germany, IQWIG considered that an added benefit was identified with the treatment of NSCLC with atezolizumab only for patient with **high PD-L1 expression**.

Renal cell carcinoma

- Negative opinion due to high expected costs:
  - In Ireland, the NCPE has issued a recommendation regarding the cost-effectiveness of nivolumab. Following NCPE assessment of the applicant's submission, nivolumab was not considered cost effective as monotherapy for the treatment of advanced renal cell carcinoma after prior therapy in adults and therefore is not recommended for reimbursement. As per data collected in our questionnaire, nivolumab was reimbursed in Ireland for this indication.
- Overall, the other opinions were favorable, with only few restrictions on the population who should receive the treatment (e.g. IQWIG did not recommended this treatment for patients previously treated with **temsirolimus**; HAS specified that their recommendation was positive for patients with **clear cells** renal cell carcinoma)

Urothelial carcinoma

- This was the indication were the highest number of negative HTA opinions was observed, especially for nivolumab for its indication as monotherapy for the treatment of locally advanced unresectable or metastatic urothelial carcinoma in adults after failure of prior platinium-containing therapy. This was mainly due the fact that no direct comparison was performed with standard of care (vinflunine and standards chemotherapies protocols) and high costs. From the questionnaire results, it was also observed that this indications had one of the highest rate for negative reimbursement decision (in 20% of the countries), and was not yet assessed in about 30% of other countries.

Hodgkin Lymphoma

- The European marketing authorisation for pembrolizumab includes 2 subpopulations of people with relapsed or refractory classical Hodgkin lymphoma:
    1. people who have had brentuximab vedotin and autologous stem cell transplant
    2. people who have had brentuximab vedotin but cannot have autologous stem cell transplant.

The NICE recommended the reimbursement only for one of these 2 subpopulations: pembrolizumab is not recommended for treating relapsed or refractory classical Hodgkin lymphoma in adults who have had autologous stem cell transplant and brentuximab vedotin. The NICE highlighted that there was no evidence directly comparing pembrolizumab with current standard care in either of the subpopulations. Indirect analyses suggest that having pembrolizumab after brentuximab vedotin may lead to longer progression-free survival than current treatment. This would increase the number of people who can have curative allogeneic stem cell transplant. It is uncertain how many people having pembrolizumab will be able to have allogeneic stem cell transplant and their long term outcomes compared with those having standard care and this is a key driver of cost effectiveness. Because of uncertainties in the clinical effectiveness and the modelling, the cost-effectiveness estimates are uncertain. Because of this, pembrolizumab cannot be recommended for routine use in the NHS.

Restrictions regarding the length of treatment

Another common restriction observed for several cancer localizations in the UK countries was the duration of treatment. Indeed, the NICE recommended the use of pembrolizumab and nivolumab for NSCLC only if stopped at 2 years of uninterrupted treatment (or earlier in the event of disease progression). Similarly, the SMC from Scotland integrated a restriction saying that treatments for NSCLC with pembrolizumab, nivolumab and atezolizumab should be subject to a 2-year clinical stopping rule (except nivolumab for squamous cell NSCLC).

3.2 Reference frameworks enabling early access to unapproved indication of innovative immunotherapies

3.2.1 General results from the questionnaire

About half of the countries (10/22, 45%) replied within the survey that they have an existing program enabling early access to innovation therapies against cancer (before marketing authorization or before extension of indication). These countries are represented in green in the map below.

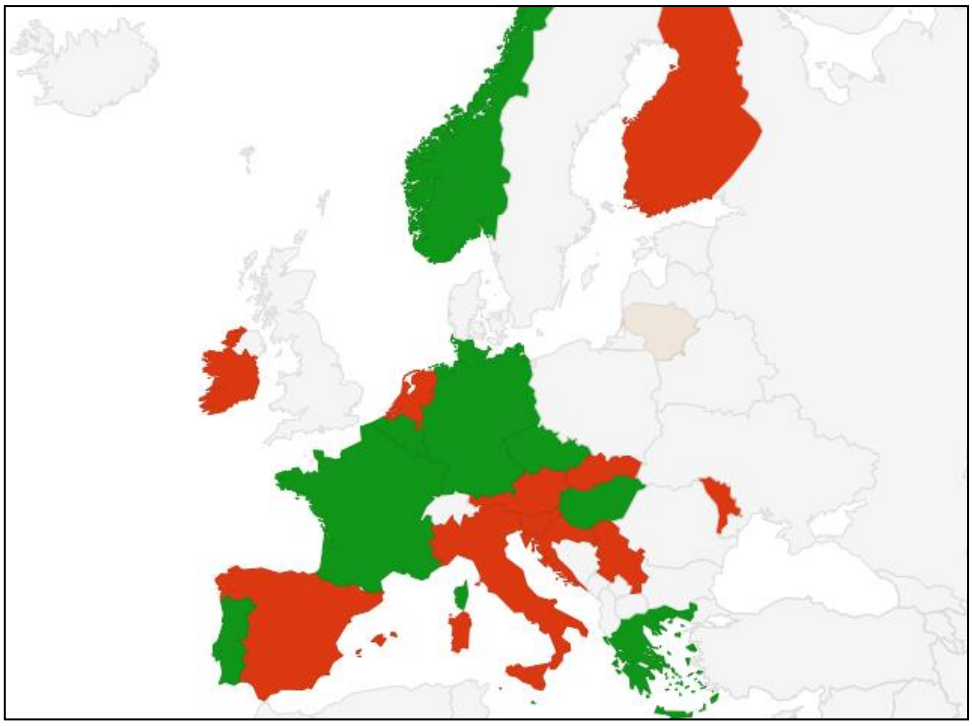


Figure 5: Graphic representation of European countries depending on the existence of a program enabling early access to innovation therapies against cancer

Programs existing: answers obtained via the questionnaire

- Portugal: “programa de acesso precoce” since June 2015: during the economic evaluation, drugs considered essentials are allowed to be used on a specific program without cost to patients, for an anticipated number of patients (managed by INFARMED, public funding)
- France: ATU, RTU, AcSé
- Germany: There are several programs in place:
    - German Consortium for Translational Cancer Research (DKTK), aim is to develop, to test and to apply innovative strategies in personalized oncology and also has a project focusing on cancer immunotherapy.
    - Several programs funded by the federal ministry of education and research focus on translation, i.e. "Innovations for individualized medicine" or the ERA Net for translational cancer research.

  These programs are under the umbrella of the Federal ministry of education and research, federal countries and the German cancer research center. Financed by the German government and federal countries.

- Luxembourg: Compassionate use is possible on a patient per patient basis, but a law is on its way which will regulate cohorts for compassionate use. Financing by industries or hospitals
- Czech Republic: specific financing from the public health insurance since 2012 for the reimbursement of highly innovative therapies (started with targeted therapies). The process of approval carried out by the State Institute for Drug Control

- Hungary: The national institute of oncology is responsible for a program since 2016 to enable access to Mekinist (trametinib: anti-MEK). The funding is private from industries.
- Greece : early access to olaparib for BRCA mutated breast cancer (managed by Astra Zeneca)
- Norway: compassioned use possible, with financing by pharmaceutical companies
- Malta: Requests for 'compassionate use' are in line with Regulation 726/2004 (authorization and supervision of medical products for human and veterinary use and establishing a European Medicines Agency) Article 83. The Superintendent of Public Health grants approval to clinicians that request such use. The medicinal product is supplied by the pharmaceutical company. This can be free of charge or otherwise purchased by the patient. Program started with the coming into force of Regulation 726/2004 Article 83.

3.2.2 Presentation of early access programs for unapproved indications

Several countries mentioned the possibility of implementing compassionate use programs which enable an early access to innovative therapies.

Other programs and regulations exist, at the national level, and some of them benefit from a public financing system in place. The programs identified through the questionnaire results are briefly described on the table below.

Table 2: Presentation of early access programs for unapproved indications identified through the questionnaire

Name of the initiative	Agency/Organization in charge of the initiative	Geographical localization	Start date	Description of the initiative	References for more information
Compassionate use programs	European regulation - European parliament and Council	Europe	2004	European regulation 726/2004 on the authorisation and supervision of medicinal products for human and veterinary use Article 83: a drug can be made available for compassionate reasons to a group of patients with a chronically or seriously debilitating disease or whose disease is considered to be lifethreatening, and who can not be treated satisfactorily by an authorised medicinal product.	https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32004R0726&from=FR
"Autorisation temporaire d'utilisation" (ATU)	ANSM - The French National Agency of Medicine and Health Product Safety	France	1994	Regulatory process for supervising early access to therapies.	https://www.ansm.sante.fr/Activites/Autorisations-temporaires-d-utilisation-ATU/Qu-est-ce-qu-une-autorisation-temporaire-d-utilisation/(offset)/0 http://www.irdes.fr/documentatio

					n/syntheses/historique-de-la-politique-du-medicament-en-france.pdf
"Temporary Recommendations for Use" (TRUs; Decree number 2012-743)	ANSM	France	May 9, 2012	Regulatory process for temporarily supervising the prescribing of drugs for indications for which they are not yet licensed	Joseph Emmerich, M.D., Ph.D., Nathalie Dumarcet, M.D., and Annie Lorence, Pharm.D. France's New Framework for Regulating Off-Label Drug Use. NEJM. 2012
AcSé clinical research program	INCa & League Against Cancer	France	2013	The aim is to offer and secure access outside the scope of a marketing authorization to therapies already approved in another indication. The treatments are studies in phase II clinical trials open to adults and paediatric cancer patientshaving experienced treatment failure and unable to benefit from an ctive clinical trial	http://www.e-cancer.fr/Professionnels-de-la-recherche/Recherche-clinique/Le-programme-AcSe
"programa de acesso precoce"	INFARMED	Portugal	2015	during the economic evaluation, drugs considered essentials are allowed to be used on a specific program without cost to patients, for an anticipated number of patients (public funding)	http://www.infarmed.pt/web/infarmed/avaliacao-terapeutica-e-economica/programa-de-acesso-precoce-a-medicamentos
"Drugs in espetial situations"	?	Spain (Catalonia)	?	Enable an early access to innovative therapies in concrete situations	
Early Access to Medicine Scheme (EAMS)	MHRA, NICE and NHS	UK	2014	The early access to medicines scheme (EAMS) aims to give patients with life threatening or seriously debilitating conditions access to medicines that do not yet have a marketing authorisation when there is a clear unmet medical need. The scheme was launched in April 2014 and demonstrates a joint commitment from government and industry in the UK to pharmaceutical innovation, providing a platform for medicines to be brought to patients at a much faster rate than ever before.	https://www.gov.uk/government/publications/early-access-to-medicines-scheme-eams-how-the-scheme-works
German consortium for translational	DKTK	Germany		Aim is to develop, to test and to apply innovative strategies in personalized oncology and also	https://www.dkfz.de/en/dktk/

Cancer Research				has a project focusing on cancer immunotherapy	
Action Plan for Individualized Medicine	Federal ministry of education and research	Germany		The Federal Ministry of Education and Research supports this relatively new branch of medicine on various levels. All six German Centres for Health Research take account of individualized medicine in their respective research fields. It is their goal that new research findings can be translated quickly into customized treatments. The Ministry also supports a wide range of projects on individualized medicine ranging from basic research to applied and clinical research. In its Action Plan for Individualized Medicine, the Ministry pools initiatives that open new perspectives both for the treatment of patients and for innovations in the health industry.	https://www.bmbf.de/en/individualized-medicine-2593.html
Modification to the amended law of 11 April 1983 regulating the market authorisation and advertising of medicinal products (Projet de loi n°7383)	Ministry of Health	Grand Duchy of Luxembourg	2020 (estim.)	An amendment to the current law is currently in preparation, and is expected to be finalised in the course of the next year. Dedicated provisions aim to complete the amended law of 11 April 1983 regulating the placing on the market and advertising of medicinal products by inserting several provisions relating to the "off label" prescription of medicinal products (occasional prescription or as part of a medical emergency program), the prescription of medicinal products for compassionate use (occasional prescription or in the context of 'a compassionate use medical program), or in case of a health emergency. The Division of Pharmacy and Medicines of the Health Directorate is engaged in the preparatory work on the amendment. A new national "Agency on Medicines and Healthcare Products" is currently being set up to oversee in the	http://sante.public.lu/fr/politique-sante/ministere-sante/direction-sante/div-pharmacie-medicaments/index.html https://www.cc.lu/uploads/tx_usercavis/5239CCL_medicaments_01.pdf

				future the early access programmes, amongst other activities.	
Specific financing system for highly innovative therapies	State Institute for Drug Control	Czech Republic	2012	Specific financing from the public health insurance for the reimbursement of highly innovative therapies (started with targeted therapies). The process of approval carried out by the State Institute for Drug Control	http://www.sukl.eu/ file:///C:/Users/hdenis/Downloads/Pricing%20and%20reimbursement%20-%20general%20information%202018%20(1).pdf

3.2.3 Additional programs facilitating early access in Europe

Table 3: Additional programs facilitating early access in Europe

Name of the initiative	Agency/Organization in charge of the initiative	Geographical localization	Start date	Description of the initiative	References for more information
PRIME scheme	European Medicine Agency	Europe	2017	PRIME is a scheme launched by the European Medicines Agency (EMA) to enhance support for the development of medicines that target an unmet medical need. This voluntary scheme is based on enhanced interaction and early dialogue with developers of promising medicines, to optimize development plans and speed up evaluation so these medicines can reach patients earlier.	https://www.ema.europa.eu/en/human-regulatory/research-development/prime-priority-medicines
Adaptive pathways	European Medicine Agency	Europe		This concept applies primarily to treatments in areas of high medical need where it is difficult to collect data via traditional routes and where large clinical trials would unnecessarily expose patients who are unlikely to benefit from the medicine.	https://www.ema.europa.eu/en/human-regulatory/research-development/adaptive-pathways
Conditional marketing authorization	European Medicine Agency	Europe		Conditional approvals are valid for one year and can be renewed annually. The holder is required to complete specific obligations (ongoing or new studies, and in some cases additional activities) with a view to providing comprehensive data confirming that the benefit-risk balance is positive. Once comprehensive data on the product have been obtained, the marketing authorisation may be converted into a standard marketing authorisation (not subject to specific obligations). Initially, this is valid for 5 years, but can be renewed for unlimited validity.	https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/conditional-marketing-authorisation
Italian algorithm for identification and boosting of innovation	AIFA	Italy		Evaluation of the innovation degree	https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0218175

3.3 Stakeholders opinion on access to innovative immunotherapies

For the analysis, results from both questionnaires were combined (questionnaire specific to access and questionnaire to clinical guidelines providers).

A first round of the survey dissemination was performed in December 2018. To increase response rate for patients, the European Cancer Patient Coalition (ECPC) launched a second round of dissemination in April 2019 through their network.

A total of 54 answers were collected from the 20 different countries cited below and for 14 answers, the country was not specified.

- Spain (5)
- France (5)
- Sweden (4)
- Italy (3)
- UK (3)
- Greece (2)
- Romania (2)
- Norway (2)
- Ireland (2)
- Germany
- Lithuania
- Latvia
- Luxembourg
- Malta
- Netherlands
- Poland
- Portugal
- Serbia
- Canada
- USA

The types of responders are presented by categories in the graph below.

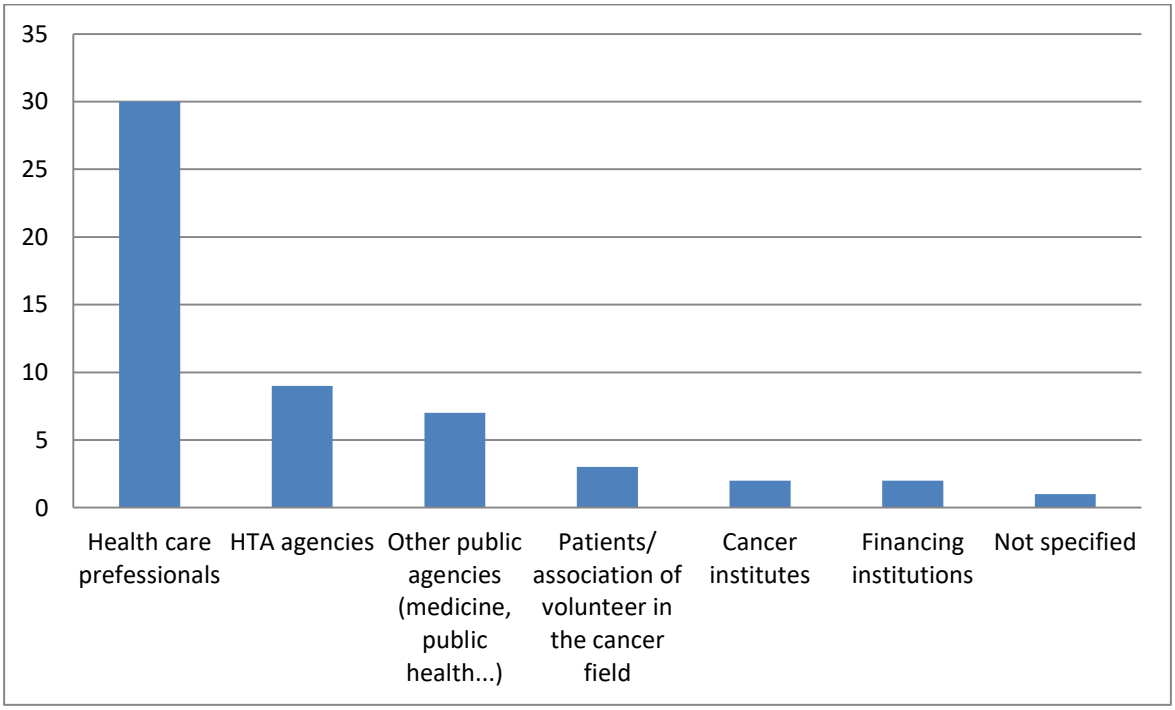


Figure 6: Presentation of the type of questionnaire responders by categories

The second round of dissemination performed by ECPC strongly increased the number of healthcare professionals replying to the questionnaire, rising from 7 to 30.

3.3.1 Reimbursement of innovative immunotherapies

55% of the respondents thought that the system in place in their country/region enabled a proper access to innovative immunotherapies in terms of reimbursement. The main negative point raised was the high cost of these therapies. Time to access was also a factor which was seen as something which could be improved in several European countries.

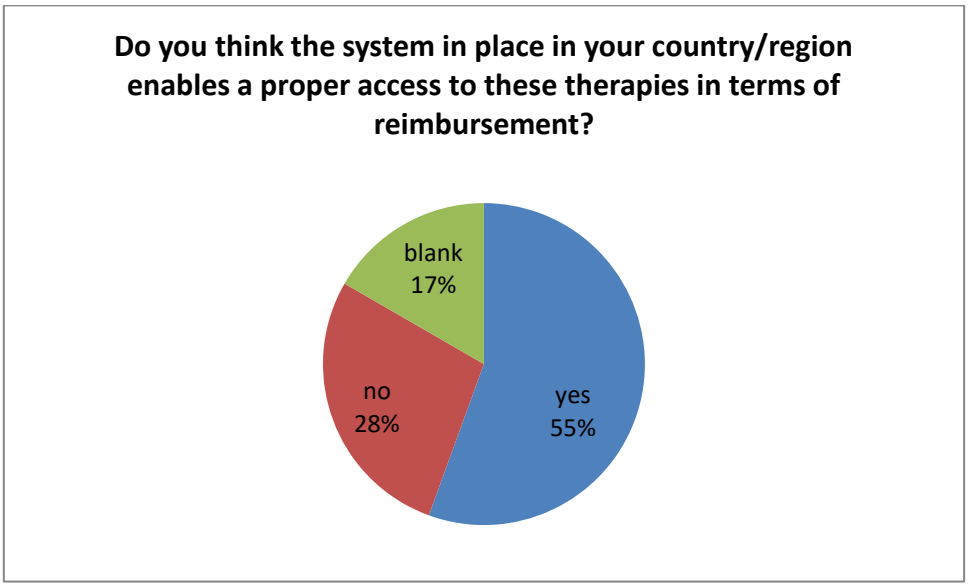


Figure 7: Presentation of the answers to the question: "Do you think the system in place in your country/region enables a proper access to these therapies in terms of reimbursement?"

Two main suggestions for improvements were made:

- Strong interactions between the different national and regional agencies seem to be important to enable access.
- Clear defined pathways and juridical frameworks seem to facilitate access to innovative therapies in terms of reimbursement

Some examples were described for positive answers:

- "Norwegian system: https://nyemetoder.no/english: the work performed benefit both to payers and to clinical guideline providers"
- Germany: "In Germany all drugs can enter the market and are reimbursed directly after regulatory approval. At the point of market entry an assessment procedure starts which aims at informing physicians and patients about the possible added benefit of the new drugs compared to standard of care and at negotiating a price based on the added benefit."
- "In France the public health care system ("social security") pays for treatments with an official authorization (AMM); innovative therapies can be paid via "compassionate use". So the situation is much better than in many other countries."
- UK: "Have been through successful HTA process"

Other comments:

- “HTA-procedures are foreseen at moment of submission for reimbursement, as well as later in time. The latter concerns revisions with update of scientific publications and real life data.”
- “Reimbursement can include managed entry agreements with pay-for-performance.”
- Norway: “There are considerable differences between the various cancer types regarding access to therapy. The national organ for decisions about reimbursement has accepted an unequal number of treatments among those available.”
- Sweden: “In order to achieve an equal, cost-effective and appropriate use of new medicines for all patients in the country, all county councils, several governmental agencies and the pharmaceutical industry collaborate in a joint process for the introduction of new medicines. This national structure is called ”Nationellt ordnat införande av nya läkemedel”, or Managed introduction.”
- “Accelerated access is making available unproven technology. Long term outcomes are unknown and procedures for gathering and assessing so-called "real world evidence" are scientifically weak and unvalidated. Patients are being experimented upon outside regulatory oversight and without proper consent.”
- Canada: “Patients who receive one checkpoint inhibitor can not have access to a second if they fail. The first car-t has been approved in Canada but is currently under negotiation- question of equal access if a major concern as only specific centers will be able to provide car-t cell therapy”.
- Romania: “Not all of those inhibitors have been approved for reimbursement.”

Additionally, one person raised that access to these therapies could also depends on the prescriber and healthcare facility and their “affinity” with these innovative therapies. In Serbia, it seems that the number of drugs available on the list for reimbursement is limited and could be increased to gain better access.

One healthcare professional in Ireland also mentioned that visibility could be increased regarding the availability of innovative immunotherapies in terms of reimbursement.

3.3.2 Early access programs

47% of the respondents mentioned that there was an existing program in their country to enable early access to innovative therapies against cancer before their marketing authorization (or before extension of indication.

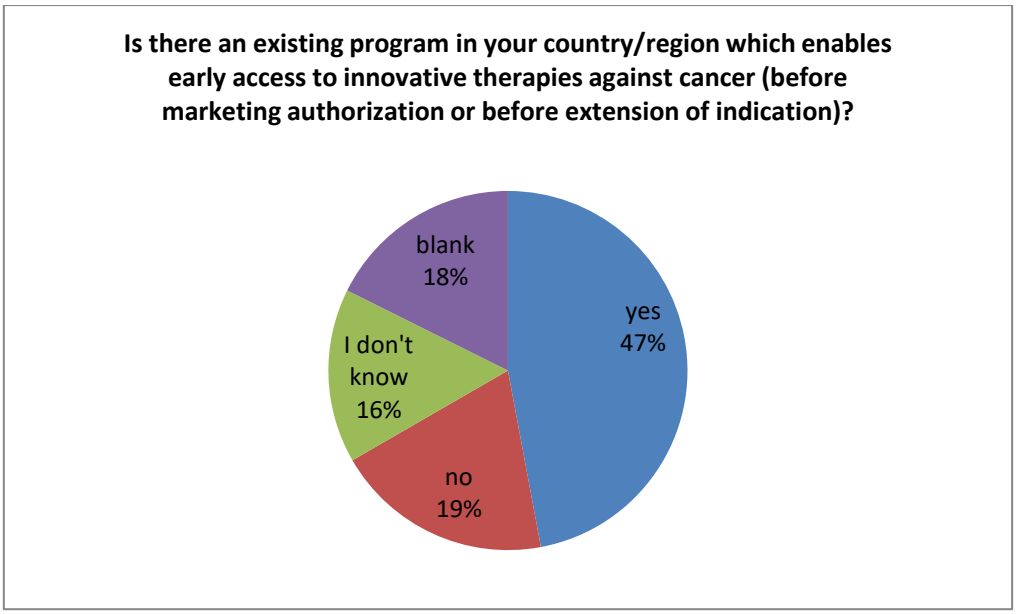


Figure 8: Responses to the question: "Is there an existing program in your country/region which enables early access to innovative therapies against cancer (before marketing authorization or before extension of indication)?"

Among the 24 positive replies mentioning that there was an existing early access program in place, most of them (almost 80%) seemed satisfied with the system implemented.

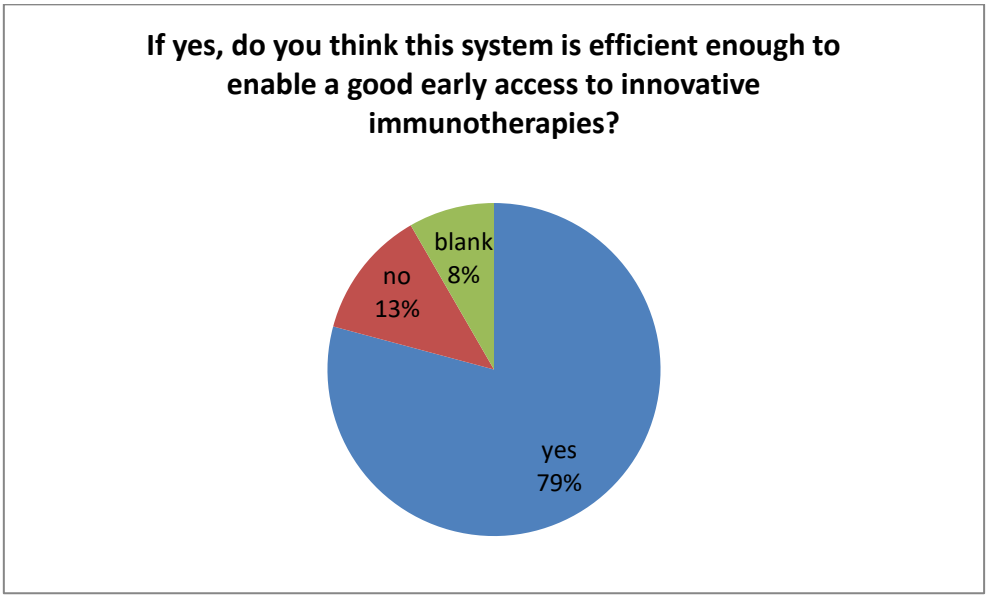


Figure 9: Responses to the question: "If yes, do you think this system is efficient enough to enable a good early access to innovative immunotherapies?"

Positive comments:

- Spain: “There is a program named "Drugs in Espetial Situations" that enable an early access to innovative therapies in concrete situations”
- Spain: “Although some improvements may be anticipated, more than 30.000 early accesses are possible in Spain every year”
- Germany: “There is no regular access to new drugs (outside clinical trials) before marketing authorization; this is protecting patients from unproven therapies. However, in exceptional circumstances, individual patient could be treated (e.g. via compassionate use programs). Once a drug is approved in one indication, there is the possibility of off-label use.”
- Unspecified country: “Standard "medical need program" and "compassionate use program""
- UK “Early Access to medicines scheme (EAMS)”
- France: “ATU and RTU system enable a good early access to innovative therapies in France”
- Greece: “country need a system that make easier and at the same time makes it more reliable to use innovative medicines for patients. reliable in terms of clinical effectiveness and real benefits for the patient, as well as cost-effectiveness.”

Negative comments:

- “early use should be very restrictive to clearly outstanding drugs”
- “Early access should be avoided. The decision of financing must be quick. Early access programs favors inequities”
- Italy: “Currently, early access to innovative cancer therapies only is possible through expanded access programs or clinical trials.”
- “I think it is not necessary. Pharmaceutical firms want to create the need of the use of new drugs as early as possible but I think that is better to finish the Phase III clinical trials than the accelerated approvals by the EMA only with phase II trials and without knowing the benefits and risks (side effects) of new drugs.”
- “Early access in itself without sufficient Information about the benefits and harms of a new treatment beyond the given possibilities does not seem to be an advantage for patients.”
- Unknown country: “There is a Protocol between the Pharma Company and Hospitals, whereby the Pharma provides medication on request made by the later. The process is not fully effective because the access is limited”
- “I am not sure I approve the early access without some considerations. It is an assigned sword. Time for sufficient R&D to be done is important, hence the regular processes should maybe be strengthened and not bypassed as I believe the early access programs sometimes may do.”

Some comments/suggestions for improvements:

- Early access programs can help for the gap between EMA approval and definition of the price as well as decision for reimbursement in member states which enable access.
- Strengthening dialogue among payers and prescribers could help with the implementation of such programs.

- Operate at a national level, so that patients can view where they can gain access to these treatments. Preferably limit the number of centers that can provide early access to ensure experienced clinicians are managing these patients, and have appropriate systems to manage and report side-effects, as well as allowing these systems to be resourced appropriately. Also so that patients can be more aware of that fact that they are receiving an unapproved treatment with poorly characterized risks and benefits. There needs to be some collaboration between payers prior to access being granted, so that there are clear pathways for continued funding for patients on treatment, in the event of a negative reimbursement decision. (from unspecified country)
- From HTA agency (unknown country): Ad hoc and controlled at local hospital rather than national level, resulting in a potential post-code lottery to access.
- It is important to consider it as an integrated process that, however, need to guide access through different phases of the medicine development (from true compassionate use of medicines that are in the very early phases of development and hence without a lot of knowledge on their value, to medicines during the interval between approval and Price and reimbursement decisions). Clear rules may help to guide this transit while providing access to patients without alternatives
- “Better HTA regulations as to allow countries such as Romania to implement immediately the access just like in Germany of U.K. where between the marketing authorization and full reimbursable access there is no big delay, and it is almost done automatically”
- Inequalities between healthcare centers and regions have been observed in several countries. A better access to specialized centers, everywhere in the country should be implemented.
- Proper procedures for post-registration evaluation and validation of treatments are needed

4 Discussion and remaining challenges

4.1 Factors leading to restrictions of uses and limitation of access to innovative therapies: how to reduce and to limit them?

4.1.1 Low evidence supporting marketing authorization

More and more innovative drugs are approved based on limited clinical evidence (due to early stage clinical trials, low number of patients enrolled, very specific target groups…). The decision for granting a marketing authorization and for approving the reimbursement of these innovative drugs can be thus quite challenging.

To compensate the early arrival on the market and early reimbursement decision, several systems have been implemented such as conditional marketing authorization and conditional reimbursement systems. This enables patients to get an early access while the health authorities and HTA agencies continue to collect and assess data related to the new therapy.

The implementation of systems enabling the long term follow-up in real-life settings such as registries is also helpful in these settings. This links to our task 4 objectives. However, having

the competent resources and systems to implement such registries and long term follow-up can be challenging for some countries.

Several limitations of uses and of reimbursement observed were also linked to some of the exclusion criteria of clinical trials (such as ECOG 0 – 1, no brain metastasis for melanoma).

4.1.2 No direct comparison data with alternative therapies

Several HTA opinions highlighted the difficulty to place innovative therapies within cancer treatment strategies due to missing direct comparison data. This was mainly observed for the indication of nivolumab for urothelial carcinoma where most of the HTA opinions published where either negative or highlighted high level of uncertainties. Indeed, there was no direct comparison performed with standard of care. From the questionnaire results, it was also observed that this indications had one of the highest rate for negative reimbursement decision (in 20% of the countries), and was not yet assessed in about 30% of other countries.

Another example was for the treatment of BRAF-mutated patients with advanced or metastatic melanoma for which a first-line treatment option with anti-BRAF/anti-MEK is available since 2015. With the more recent arrival of anti-PD-1 which could be available for these same patients as another first-line treatment option, it raises the question of which one to include as first line, especially when there is no data comparing these 2 treatment options directly.

As suggested in the other task 1 deliverable, the implementation of a public financing system to pilot studies comparing innovative therapies between them could help solving these situations.

4.1.3 High costs related to innovative therapies

Lots of HTA opinions advised reduction of prices of these innovative therapies to facilitate their integration into clinical practices. Indeed, some countries did not accept the reimbursement of these therapies due to high costs issues. This leads to reduce access to certain therapies for some countries.

The Organisation for Economic Co-operation and Development (OECD) has published a report on pharmaceutical innovation and access to medicines in November 2018. This report reviews the important role of medicines in health systems, describes recent trends in pharmaceutical expenditure and financing, and summarizes the approaches used by OECD countries to determine coverage and pricing. This report shows that the increasing prices of innovative medicines are linked with several issues for policy makers, such as concerns about the value of spending in some therapeutic areas; challenges in anticipating the arrival of very effective medicines for highly prevalent diseases and sharp price increases in off-patent products. Some of the main challenges raised by the OECD:

- High expenditures associated with innovative therapies not always reflecting the actual health benefit
- Need for better anticipate innovative therapies
- Unexpected and sudden rising prices have led to reduction of access in certain countries

4.2 Reference frameworks enabling early access to innovative therapies: What is good and what could be improved?

Early access decisions can be very difficult to take due to the limited clinical evidence available to assess the benefit-risk ratio. As per the questionnaire replies, we could see that comments provided were quite various. Some of them were very positive and gave positive feedback on existing systems which seem to be quite efficient to provide early access for unapproved indications (such as ATU and RTU in France and EAMS in UK). It was seen as a good potential system to bridge the gap between the granting of EMA approval and the decision for reimbursement.

On the other side, several persons reminded that it was important to limit these kinds of programs only to very promising drugs/indications and for patients who would have no other therapeutic opinion.

Overall, for the implementation of frameworks and programs to enable early access for an unapproved indication of an innovative therapy, two main aspects stood out:

1) The need to have clear defined pathways and frameworks;
2) The need to have strong discussion among the different stakeholders.

These 2 points are being further discussed hereafter.

4.2.1 Clear defined pathways and frameworks

Clear defined pathways and juridical frameworks seem to facilitate access to innovative therapies in terms of reimbursement as suggested by several persons through our questionnaire. It was also suggested to have national programs rather than local ones to avoid inequities between regions and healthcare centers. This would also increase the visibility of accessible drugs through this type of programs for patients.

The introduction of the European laws and regulations set by the European Medical Agency for compassionate use in the European Union helped to favor the implementation of this type of early access programs. The article 83 of Regulation (EC) No 726/2004 introduces the legal framework for compassionate use in the EU for medicinal products eligible to be authorized via the Centralized Procedure, stating that "By way of exemption from Article 6 of Directive 2001/83/EC, MS may make a medicinal product for human use belonging to the categories referred to in Article 3(1) and 3(2) of Regulation (EC) No 726/2004 available for compassionate use".

Previously, clinical trials were the only option for using unauthorized medicinal products. Compassionate use programs created a treatment option for patients in the European Union suffering from a disease without existing satisfactory authorized therapy alternatives or who could not be part of a clinical trial. The EMA recommends compassionate use through the Committee for Medicinal Products for Human Use (CHMP) and with a legal framework.

In addition, the need to make sure to have clear patient pathway and clear reimbursement strategies for patients would be receiving the drug in case of a negative decision for reimbursement seemed very important to anticipate.

4.2.2 Strengthen discussion between stakeholders

Having a good dialogue between the different stakeholders who are involved in the access to medicines pathway was seen as an important factor to improve the different programs which could be implemented at the national level.

In Sweden, there is a national structure dedicated to the introduction of innovative drugs. This national structure, called “Nationellt ordnat införande av nya läkemedel”, brings together county councils, several governmental agencies and the pharmaceutical industry. Working jointly in this kind of well-established structure seems to facilitate the introduction of new medicines.

A review of existing compassionate use programs in the European member states was published by Balasubramanian *et al* in 2016. They identified 20 countries in Europe where compassionate use programs were existing. However, as highlighted in their publication, denomination and definition of such programs can be very various from one country to another (e.g. special access programs, named patient programs, managed access programs…). This shows the importance to have a good communication between the different stakeholders to make sure that the understanding is the same for everyone.

4.3 Inequalities across European countries regarding the access to innovative immunotherapies: how to reduce them?

4.3.1 Variation in terms of time to access

The questionnaire results showed that some countries had already access to innovative immunotherapies very shortly after EMA approval whereas other still don’t have access 2 years after approval.

The German system seem to enable the fastest system: in Germany all drugs can enter the market and are reimbursed directly after EMA approval. At the point of market entry an assessment procedure starts which aims at informing physicians and patients about the possible added benefit of the new drugs compared to standard of care and at negotiating a price based on the added benefit.

4.3.2 Increase collaboration between healthcare system players seem to benefit patients for access

Some comments obtained thought our questionnaire suggested that strong interactions between the different national and regional agencies seem to be important to facilitate the access to innovative immunotherapies.

In Norway, the National System for Managed Introduction of New Health Technologies has been implemented since 2013. The work performed on HTA benefit both payers and clinical guideline providers. To optimize the process for introduction of new medicines, it was decided to conduct Single Technology Assessments (STAs) on all new drugs and indications from October 2015. In this way the system achieved an improved predictability and efficiency aiming to complete STA reports as near in time as possible of the marketing authorization.

Horizon scanning reports are used as a basis to identify which drug could be reviewed. The Norwegian Directorate of Health is responsible for the national clinical guidelines. To reduce and avoid duplication of work the national HTAs are to be used both in decision making and in the work with national guidelines. Whenever there is as decision on a method that is a subject to a national guideline, the decisions made at the national level shall be implemented in it. This is a good example of strong communication between all stakeholders involved for the arrival of a new drug on the market.

Some countries share resources in order to optimize the review of innovative therapies. For instance, in Wales, medicines funded by the NHS Wales follow guidance from two sources, the National Institute for Health and Care Excellence (NICE) and the All Wales Medicines Strategy Group (AWMSG). The AWMSG does not always conduct its own entire review if the work has already been performed by the NICE.

The BeNeLuxA initiative aims to increase the efficiency of the assessment, pricing and reimbursement of medicines by exchanging expertise and by mutual recognition of Health Technology Assessments. Four types of collaboration are being studied in the Beneluxa initiative:

- Re-use of Health Technology Assessment (HTA) reports
- Joint writing of an HTA report: Authors of several countries join forces in order to write one report. This report can be used in all countries involved.
- Mutual recognition of HTA reports: in this case, large parts of, or even a full, HTA-report of one country are adopted by others in a parallel process. The results of the assessments are then published at the same time.
- External referee: HTA institutes of the various countries can also act as each other's external referees in national procedures. It does not involve active work in a Health Technology Assessment itself.

More information are available on the BeNeLuxA website (http://beneluxa.org/hta).

Furthermore, The EUnetHTA network also works on joint HTA assessment. Through the joint action, their goals are to promote good practices in HTA methods and processes and to create a sustainable system of HTA knowledge sharing.

4.3.3 Control rising prices

A publication of the actual prices of drugs was published early 2016 showing the disparities of actual prices across European countries. This shows the importance to increase collaboration between European countries to avoid high increase of innovative medicine prices.

There are already some European initiatives aiming at raising awareness regarding the disparities in terms of access to anticancer drugs. The European Cancer League has a dedicated task force on access to medicines for instance. They published a white paper highlighting the main challenges on this issue in October 2018.

Furthermore, joint negotiations of prices between several countries have been initiated for instance through the BeNeLuxA initiative as well as under the EUnetHTA joint action.

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