iPAAC
INNOVATIVE PARTNERSHIP
FOR ACTION AGAINST CANCER

Co-funded by
the Health Programme
of the European Union

Innovative cancer therapies in clinical practice guidelines

Deliverable WP9 – Task 1 (part 1)

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Version:	3.0
Date:	06. 12. 2019

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This report arises from the Innovative Partnership for Action Against Cancer Joint Action, which has received funding from the European Union through the Consumers, Health, Agriculture and Food Executive Agency of the European Commission, in the framework of the Health Programme 2014-2020. The content of this report represents the views of the author/s only and is his/her/their sole responsibility; it cannot be considered to reflect the views of the European Commission and/or the Consumers, Health, Agriculture and Food Executive Agency or any other body of the European Union. The European Commission and the Agency do not accept any responsibility for use that may be made of the information it contains. The authors are not responsible for any further and future use of the report by third parties and third-party translations

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
EMA	Eropean Medicine Agency
ESMO	European Society of Medical Oncology
EU	European Union
FDA	Food and Drug Administration
GoR	Grade of Recommendation
HSCT	Hematopoietic Stem Cell Transplantation
INCa	French National Cancer Institute
iPAAC	Innovative Partnership for Action Against Cancer
JRC	Joint Research Center (of the European Commission)
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
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, aimed to highlight challenges associated with the integration of innovative therapies into clinical practice guidelines. For this purpose, the WP9 started by conducting a mapping of clinical practice guidelines which were positioning innovative immunotherapies in cancer therapeutic strategies. The focus was given to the most recent immunotherapies, *ie.* checkpoint inhibitors and CAR-T cells. Difficulties for positioning these innovative therapies in the therapeutic strategies were identified; off-label recommendations, as well as recommendations associated with biomarkers were also highlighted. Then, the WP9 aimed to point out methodological considerations and programmes which could be implemented in order to surpass these challenges.

Method

For this purpose, a literature review was performed and 2 questionnaires were sent out: the first one among iPAAC partners to get a better understanding in national practices around guidelines in the oncology field; the second questionnaire was sent to WP9 partners and organizations in charge of guidelines writing.

Results

Brief description of guidelines

A total of 120 guidelines positioning checkpoint inhibitors and/or CAR-T cells were identified, including 52 from European organizations. Most of them included mainly adults in the scope, except one consensus agreement for elderly and one focusing on the paediatric population. Among these 120 guidelines, 22% (N=26) were from 8 different institutional organizations, 32% (N=38) from cancer societies / associations of healthcare professionals and 31% (N=37) from oncology networks / cancer centres. Besides, 19 guidelines were produced from collaborations between several organizations.

One of the specificity of checkpoint inhibitors is the very large number of localizations in which these therapies were tested and approved. This explains the various localizations identified among guidelines analysed, with a larger number for oldest approved indications such as melanoma (15 guidelines), lung cancer (15 guidelines) and kidney cancer (13 guidelines). The anteriority of the marketing authorization does not guarantee the number of recommendations issued: there were more guidelines placing checkpoint inhibitors for the most recent indication for bladder cancer (8 guidelines), rather than for head and neck cancer (3 guidelines) and for Hodgkin lymphoma (5 guidelines).

Most of the countries in Europe seem to have existing organizations in charge of writing clinical practice guidelines in the field of cancer. However, only half of them had already included these therapies within the guidelines at the time of the survey, 7 years after the approval of the first checkpoint inhibitor in Europe (ipilimumab) and 3 years after the introduction of nivolumab and pembrolizumab. It was also highlighted through this WP work that **the visibility of existing European national/regional clinical practice guidelines could be improved.** Indeed, only 20 out of the 120 guidelines selected were identified though the initial PubMed search. **The barrier of language could explain part of this limited visibility.** Indeed, the WP9 questionnaire showed that 90% of national/regional guidelines are published in national languages. **When experts were consulted to define the most efficient way to communicate the release of a new or**

updated guideline, responses were quite various, going from publications on the organization's website to communication at congresses, scientific publications and emails addressed to professional societies. However, most of them thought that it would be helpful to have a guidelines repository to better identify existing guidelines in Europe.

Off-label recommendations

Among the 120 guidelines analysed, 18 were providing recommendations for an indication not approved by the referenced medicine agency, 9 were describing clinical results for an unapproved indication, 5 were referring to an off-label indication and 8 recommended inclusion into clinical trials for an unapproved indication. The most widespread off-label recommendation was for the use of checkpoint inhibitors, particularly pembrolizumab, for MSI-H tumours, and more especially for MSI-H colorectal tumours. Indeed, 4 out of the 7 guidelines for colorectal cancer including checkpoint inhibitors in the colorectal cancer treatment strategy were from European organization whereas there was no authorized indication approved in Europe at the time of the analysis.

There was some divergence of opinion regarding the acceptability of providing recommendations for off-label indications. Several experts agree to say that there are situations for which off-label recommendations could be tolerated in a clinical practice guideline, especially for small groups of patients, specific biomarker expression, paediatric population, or when there is no other therapeutic alternative. However, from governmental body and national agency it seems to be harder to include off-label recommendations in CPG than for medical societies. Whatever it is noteworthy that Companies do not systematically revendicate some well-recognized indications, especially in relatively unfrequent diseases.

Disagreement between guidelines regarding cancer treatment strategies

When several innovative therapies are developed in parallel, it can be hard to obtain comparative data between these new therapies. This leads to difficulties to define the best place within the cancer treatment strategy and consequently to differences between guidelines regarding the positioning of these therapies. This was the example for BRAF-mutated patients with unresectable or metastatic melanoma who could receive either anti-BRAF/anti-MEK or anti-PD-1. There is currently no clear evidence comparing the efficacy and safety of these 2 treatment options as they were developed in parallel. It is thus hard to define whether one treatment option should be preferred over the other one. **The experts thought for a large majority of them (90%) that a public fund financing studies comparing innovative therapies between them could be helpful to better define their place in cancer treatment strategies.**

Production and update of guidelines

Some ideas were suggested to improve the length of production and update of guidelines such as the support from robust methodology, standardized operational procedures, dedicated in-house staff with methodological expertise, reduction of the scope of guidelines, strengthen the training on methodological approach for medical doctors and experts involved in the production of guidelines, increasing financial support. Strengthen collaboration appear as a good tool, especially for rare types of cancers and therapeutic areas where no specific society exists. The implementation of endorsement systems could also be a good option as long as clear procedures exist to structure the work and with a strong involvement both from the organization writing and from the one endorsing the guideline.

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 partners including: the European Society for Medical Oncology (ESMO), the American Society of Clinical Oncology (ASCO), the French Association of Urology (AFU), the Italian Association of Medical Oncology (AIOM), 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 first task aimed to point out challenges associated with the integration of innovative therapies into clinical practice guidelines. Difficulties for positioning these innovative immunotherapies in the therapeutic strategies were identified with the help of the realization of a mapping of existing clinical practice guidelines including innovative immunotherapies in cancer treatment strategy. Off-label recommendations, as well as recommendations associated with biomarkers were also highlighted.

The WP9 then collected feedback from partners and experts regarding the issues raised around clinical practice guidelines. The goal was to point out methodological considerations, collaborations, programs and other potential solutions which could be implemented in order to surpass these challenges.

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 systematic 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. The results will be presented by cancer localization as it was agreed to have an approach by disease rather than by molecules. If other innovative immunotherapies would be referred in guidelines, it would be assessed at the disease level.

In order to get a good understanding of the difficulties encountered in clinical practice guidelines for checkpoint inhibitors and CAR-T cells, the WP9 conducted a mapping of the existing clinical practice guidelines positioning these specific medicines. An Excel table gathering all clinical practice guidelines was built with a quick assessment for each guideline.

Due to the very fast evolution of immunotherapies indications and thus of clinical practices, it is not possible to maintain the table up to date. The WP9 considered that the mapping performed at a given time (summer 2018) would provide sufficient knowledge regarding issues and challenges encountered to integrate these immunotherapies into clinical practice guidelines. For the purpose of the roadmap, the WP9 could however maintain the list of the European clinical practice guidelines **providers** up to date.

2.1 Identification of clinical practice guidelines positioning innovative immunotherapies

2.1.1 PubMed search & optimization of the equation of search

Several combinations of key words and MeSH terms were tested in order to optimize the equation of search. All the equations tested are presented in appendix 1. The aim was to retrieve the most important guidelines, to identify guidelines writers and to have a first idea of existing recommendations, including recommendations in potential off-label localizations.

The following equation of search was chosen:

("neoplasms"[MeSH Terms] OR cancer[Text Word] OR "Hematologic Neoplasms"[Mesh] OR "Lymphoma"[Mesh]) AND (Immunotherap* OR checkpoint inhibitor OR PD-1 OR PD1 OR PD-L1 OR PDL-1 OR PDL1 OR CTLA-4 OR CTLA4 OR Ipilimumab OR nivolumab OR pembrolizumab OR atezolizumab OR avelumab OR durvalumab OR CAR-T cells OR CAR

OR CART OR Chimeric antigen receptor OR adoptive T cell therapy OR adoptive cellular immunotherap* OR Tisagenlecleucel OR axicabtagene ciloleucel OR gene therap*) AND (English[lang] OR French[lang]) AND ("2011/01/01"[PDAT] : "2018/08/08"[PDAT])

English and French were the spoken language of the team of INCa. This explains our choice to have only included these 2 languages in our equation of search.

With filters on publication type: Consensus Development Conference, Guideline, Practice Guideline, Consensus Development Conference, NIH

The following exclusion criteria were applied:

- Non-innovative immunotherapies: molecules approved before 2011 or approved after 2011 but with a mechanism of action similar to a drug already approved before 2011
- Guidelines not assessable (barrier language, no abstract available)
- Recommendations not directly related to cancer
- Recommendations not dealing with cancer treatment strategy
- Recommendations in the veterinary field

2.1.2 Retrieval of the most updated version of the identified guidelines

Some guidelines are updated online very often and the updates are not always published. This is why for each guideline identified on PubMed; we made sure to obtain the most updated version by verifying directly on the guidelines publisher's website. Only the most updated versions of guidelines were kept for the analysis. This also helped us to avoid duplicates.

2.1.3 Broader search to screen potential additional guidelines

In order to be more exhaustive, we also performed a deeper search in all websites of the societies identified as authors with the initial PubMed search. All guidelines published on these websites were reviewed and added to the selection if relevant. The same inclusion and exclusion criteria as for step 1 were applied at this stage.

As some authors publish their guidelines only on their websites, we have completed the screening of clinical practice guidelines with an open search on Google and the websites from other well-known Cancer Societies (eg: ASCO, NICE …) and cancer networks such as NCCN. The list of all sites consulted is available in the appendix 4.

2.1.4 Questionnaire

A first questionnaire was sent to the iPAAC partners in order to identify potential additional authors of clinical practice guidelines in European countries and to better define the place of innovative immunotherapies within clinical practice guidelines in Europe The partners were invited to describe additional guidelines whatever the language used. This allowed to complete our systematic review.

2.2 Analysis of guidelines

2.2.1 Scope of guidelines

For each guideline identified, the place of innovative immunotherapies was described and the following information was collected into an Excel table:

- Authors
- Date of publication
- Language
- Scope (disease/localization)
- Immunotherapies concerned
- Public targeted
- Key recommendations and publications supporting these recommendations
- Methodology standards
- Biomarkers

2.2.2 Position of innovative immunotherapies in the cancer treatment strategies

For each clinical practice guidelines, the place of innovative immunotherapies was characterized. Specific conditions which could have an impact on the position of the immunotherapies in the cancer treatment strategy such as the expression of a biomarker, a specific previous treatment were described.

2.2.3 Assessment of off-label recommendations

The European Medicine Agency (EMA) marketing authorizations were taken as a reference for the evaluation of the off-label recommendations. As the review was mainly performed over the summer 2018, the indications taken into account were from July 2018 (or otherwise specified in the text).

Off-label recommendations were divided into different categories:

- Clear off-label recommendations: when there was no approved indication by the reference medicine agency;
- Recommendations considered off-label in Europe, but based on FDA approved indications, in American guidelines. This category was added as several guidelines from the United States were identified in order to highlight potential differences in terms of marketing authorization between Europe and United States;
- Description of clinical trials results for an unapproved indication;
- Phrase referring to off-label indication / Allusion to immunotherapies for unapproved indication;

- Recommendation for inclusion into clinical trials for unapproved indication was also collected. This is not an off-label recommendation but it supports the relevance of assessment of the unapproved indication.

2.2.4 Identification of other potential challenges linked with the integration of innovative immunotherapies into clinical practice guidelines

For the purpose of the roadmap, other aspects of the guidelines were analysed such as:

- Recommendations linked to length of treatment and dosing schedule
- Timelines between marketing authorization and release of guidelines
- Methods for production and update
- Visibility and communication of clinical practice guidelines

The challenges and difficulties pointed out served as a support to build the second questionnaire and were further investigated with the help of feedback collected from clinical practice guidelines providers and writers.

2.3 Collection of stakeholder opinion

A second questionnaire was sent to the relevant stakeholders involved in the production of clinical practice guidelines such as:

- Cancer societies
- Association of healthcare professionals
- Oncology institutes

This second questionnaire aimed to:

- Complete the mapping of the clinical practice guidelines;
- Collect stakeholder opinions on the points of interest identified through the analysis of the clinical practice guideline:
    - How can we improve timelines for production and update of clinical practice guidelines?
    - Off-label recommendations: what is acceptable or not?
    - Position of immunotherapies in cancer treatment strategies: how can we do when we are missing comparison data?
    - How to improve the visibility and the accessibility of clinical practice guidelines
- Support the elaboration of the Roadmap

3 Results and discussion

3.1 General results from the literature review

3.1.1 Clinical practice guidelines screened

51 references have been identified thanks to the PubMed search. From these 51 references, 28 were excluded for the following reasons: guidelines referring to non-innovative immunotherapies (n=10), recommendations not related to cancer treatment strategies (n=13), recommendations not directly related to cancer (n=2), guidelines not assessable (n=1), recommendations in the veterinary field (n=1), no recommendation provided (n=1). Furthermore, 3 duplicates were identified: there were 3 references corresponding to the NCCN guidelines for melanoma, and 2 references corresponding to the SEOM clinical guidelines for the treatment of kidney cancer / renal cell carcinoma. Thus, we have kept only the most updated versions.

This diagram also shows the repartition of clinical practice guidelines identified by localizations.

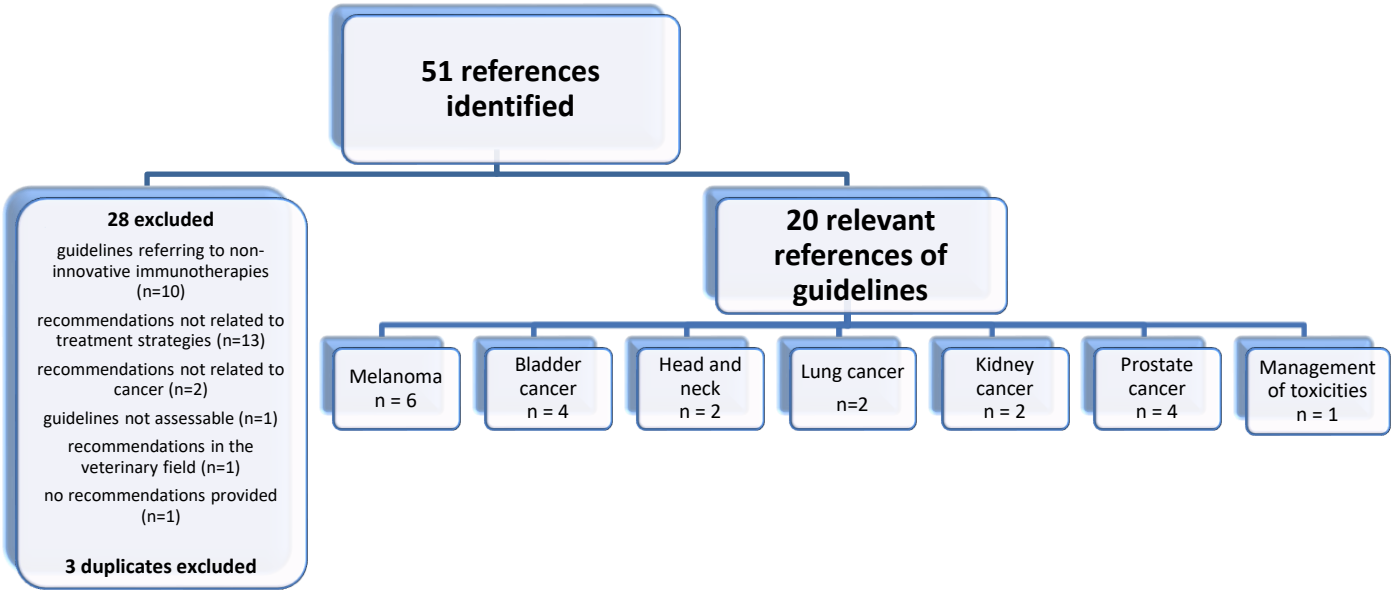


Figure 1: Clinical practice guidelines obtained with PubMed search

10 authors were identified from the PubMed search:

- SEOM: Sociedad Espaňola de Oncología Médica – Spanish Society for Medical Oncology
- NCCN: National Comprehensive Cancer Network
- ESMO: European Society for Medical Oncology

- SITC: Society for Immunotherapy of Cancer
- CC-AFU: Comité de Cancérologie de l'Association française d'urologie – French Urology association – Oncology committee
- SOGUG : Spanish Oncology Genitourinary Group
- EECP: European Expert Consensus Panel for metastatic castration-resistant prostate cancer (21 experts)
- INCa : Institut National du Cancer (France) – French National Cancer Institute
- AUA : American Urology Association
- European consensus for cutaneous melanoma : EDF (European Dermatology Forum), EADO (European Association of Dermato-Oncology), European Organization of research and treatment of cancer (EORTC)

The number of guidelines identified with the PubMed search for each author is presented in the graph below.

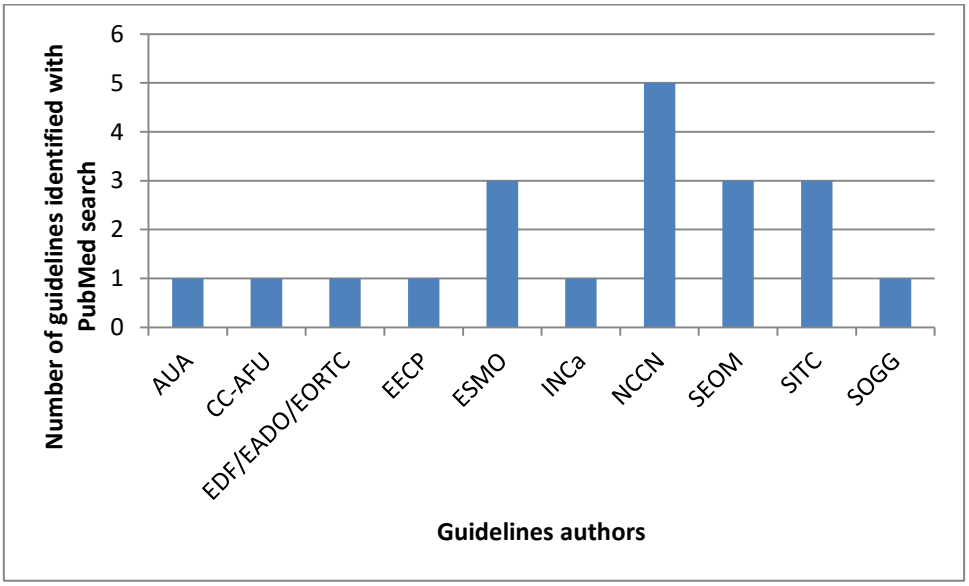


Figure 2: Number of guidelines identified with the PubMed search by authors

Among the 20 references of guidelines kept for analysis, we identified a most updated version for 10 of them. Most of them (n=5) were NCCN guidelines, which are updated several times a year.

Websites from each author identified were carefully screened to identify potential additional guidelines. This extended screening research permitted to find a large number of additional clinical practice guidelines positioning at least one innovative immunotherapy in cancer treatment strategies.

In total, after removal of duplicates and out dated versions, 120 documents were identified from this initial search.

3.1.2 Authors of clinical practice guidelines

Three main categories of authors have been identified: institutional organizations, cancer societies /organ-specific societies (including associations from healthcare professionals) and oncology networks. In addition, several types of collaborations have been identified. The distribution of the guidelines is presented by categories of authors on the graph below.

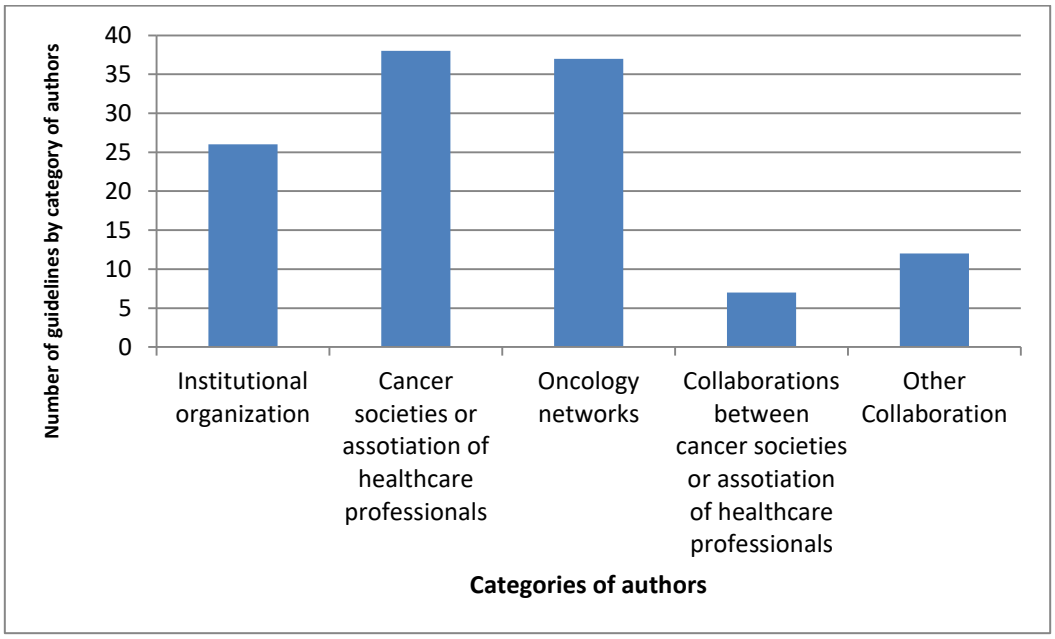


Figure 3: Distribution of clinical practice guidelines by type of authors

Guidelines from institutional organizations

Eight different institutional organizations who wrote guidelines including innovative immunotherapies in cancer treatment strategies have been identified. The names and numbers of guidelines produced by institutional organizations are presented on the graph below.

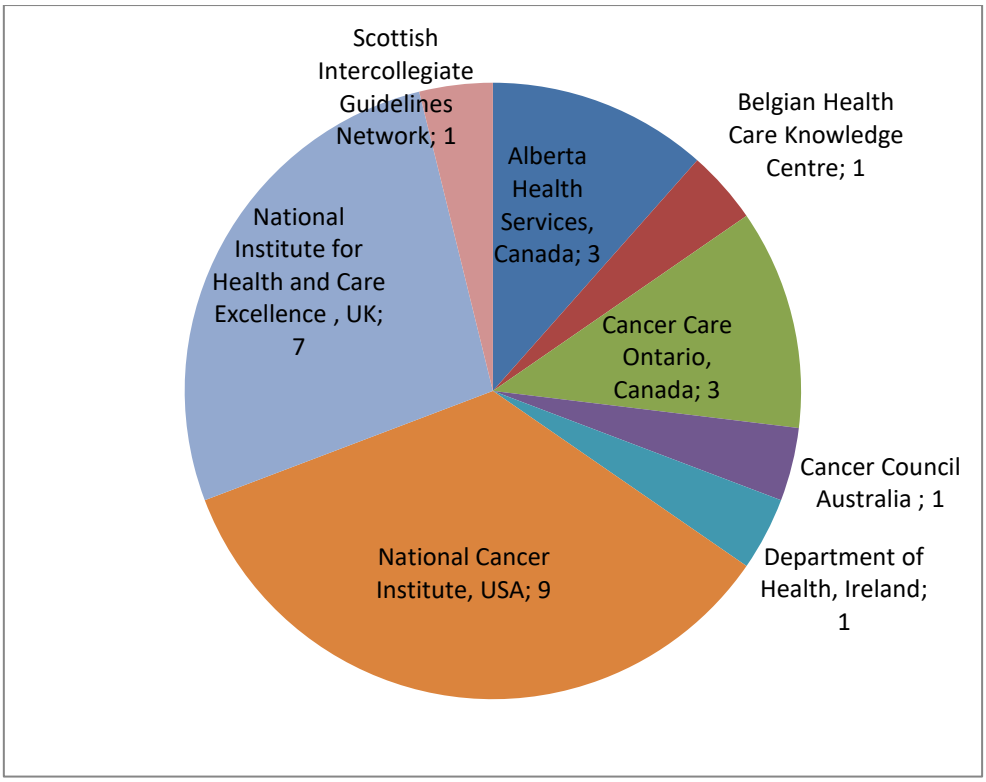


Figure 4: Number and distribution of clinical practice guidelines from institutional organizations

Comments:

- The NCI provides information ("PDQ Cancer Information") rather than recommendations. This is a source of information and of reference for healthcare professional, but the methodology of production is different than clinical practice guidelines. The level of evidence has been assessed for each treatment option, but as there are no clear recommendations provided, and there is no grading of recommendation.
- NICE pathways are constructed from technology appraisal guidance, but they do provide recommendation and position in cancer treatment strategies.
- INCa does not appear here: the guideline identified in Pubmed was replaced by the most updated version written by the French society of dermatology under the label procedure of INCa (included in guidelines written in collaboration).
- Additionally, the INC Luxembourg had an ongoing drafted version for melanoma.

Guidelines from cancer societies and other associations of healthcare professionals

The table below presents cancer societies and associations of healthcare professionals which have written guidelines placing innovative immunotherapies in the cancer treatment strategy.

Table 1: Cancer societies and associations of healthcare professionals which have written guidelines placing innovative immunotherapies in the cancer treatment strategy

Cancer societies / Associations of Healthcare professional	Number of guidelines
ESMO - European Society for Medical Oncology	12
AASLD - American Association for the study of Liver Diseases	1
AUA - American Urological Association	1
ANOCEF - Association of French speaking neuro-oncologists	1
ASCO - American Society for Clinical Oncology	4
CC-AFU - Oncology committee of the French Association of Urology	3
EASL - European Association for the study of the Liver	1
EAU - European Association of Urology	2
European Expert Consensus Panel	1
IASLC - International association for the Study of Lung Cancer	1
SEOM - Spanish Society of Medical Oncology	3
SIOG - International Society of Geriatric Oncology	1
SITC - Society for Immunotherapy of Cancer	5
SDF - French Society of Dermatology	1
SOGUG - Spanish Oncology Genitourinary Group	1

Guidelines from oncology networks and cancer centers

37 guidelines produced by networks of cancer centers referring to innovative immunotherapies have been identified including 32 from the American National Comprehensive Cancer Network (NCCN). The others were written by French regional oncology networks (AURA (n=3), ONCOMIP (n=1), Onco-Occitanie (n=1)).

Guidelines from several authors

The table below presents the collaboration between several societies or associations of healthcare professionals which triggered the production of a CPG positioning innovative immunotherapies within the cancer treatment strategy.

Table 2: Collaborations between cancer societies and/or associations of Healthcare professional producing guidelines

Collaborations between cancer societies and/or associations of Healthcare professional producing guidelines	Number of guidelines
AUA - American Urological Association ASCO - American Society for Clinical Oncology ASTRO - American Society for Radiation Oncology SUO - Society of Urologic Oncology	1
AUA - American Urological Association SUO - Society of Urologic Oncology	1
ANOCEF - Association of French speaking neuro-oncologists French Sarcoma group	1
ESMO - European Society for Medical Oncology ESO - European School of Oncology	1
ESMO JSMO - Japanese Society of Medical Oncology	1
EDF - European Dermatology Forum EADO - European Association of Dermato-Oncology EORTC - European Organization for Research and Treatment of Cancer	2

Other types of collaborations have been identified and are presented in the table below.

Table 3: Other types of collaborations producing guidelines

Collaborations	Number of guidelines
American Society for Clinical Oncology in partnership with Cancer Care Ontario	1
Cancer Council Australia in partnership with Melanoma Institute Australia	1
CKCF - Canadian kidney Cancer Forum	1
GEOQ - Groupe d'étude en oncologie du Québec DGC - General direction of oncology - Ministry of Health and social services INESSS - National institute for excellence in health and social services	1
French National thesaurus for digestive oncology (gather the following French groups: FFCD, Unicancer, GERCOR, SFCD, SFRO, SFED, SNFGE)	5
French society of dermatology (SFD) : endorsement by the French National Cancer Institute INCa (label procedure)	1
Collaboration between French regional oncology networks - OncoLogik	2

3.1.3 Description and scope of guidelines

Among the 120 documents assessed, 100 were in English, and 20 in French. It gathered both clinical practice guidelines and consensus statements. The geographical distribution of authors is detailed on the graph below.

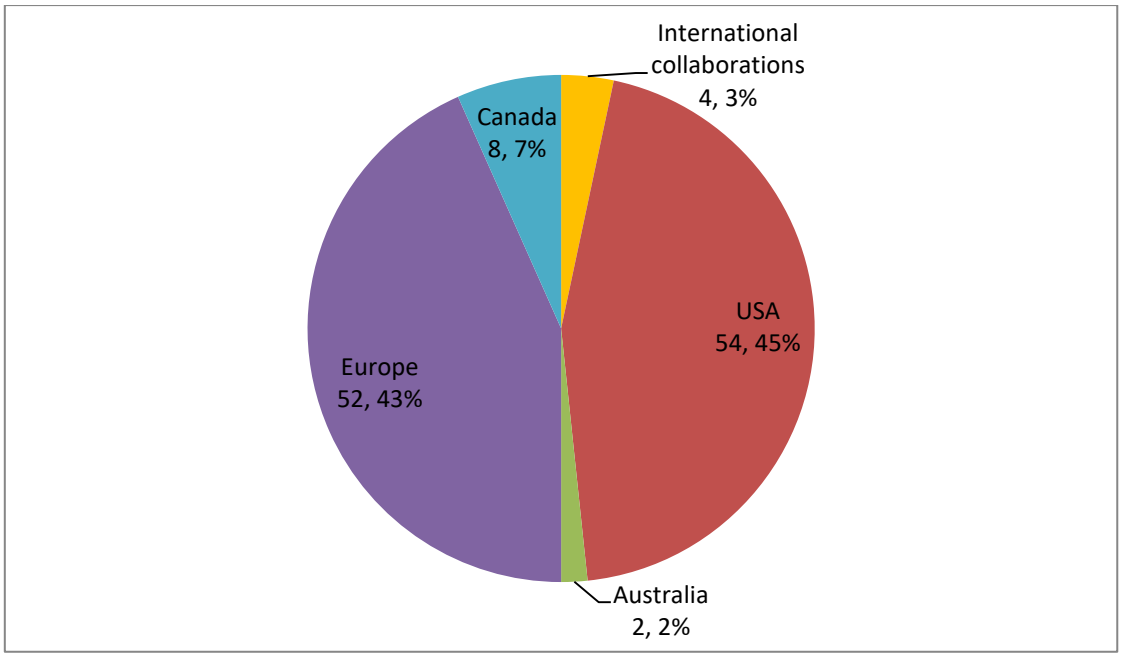


Figure 5: Geographical distribution of clinical practice guidelines authors

Among the 4 guidelines from international collaborations, the following authors were found:

- 1 collaboration Europe / Asia (ESMO & Japanese society for medical oncology);
- 1 collaboration USA / Canada (ASCO & Cancer Care Ontario);
- 1 from the International Society of Geriatric Oncology;
- 1 from the International association for the Study of Lung Cancer.

The scope of guidelines differs between organizations and between clinical practice guidelines. For instance, some organizations have gathered recommendations in one document for the management of a large disease (eg: skin cancer, lung cancer), whereas other are more specific to a subtype of cancer (eg: non-small cell lung cancer, cutaneous melanoma), or even more specific to specific stages (eg: earlier stages or metastatic disease).

About half of the guidelines included the overall management of the disease, including diagnosis, follow-up whereas the other half focused only on the treatment options.

Most of the guidelines provided recommendations for adults. Only one consensus statement from the International Society of Geriatric Oncology was dedicated to the elderly patients with metastatic renal cell carcinoma, and one document from the NCI to the treatment of childhood acute lymphoblastic leukemias.

Four guidelines were dealing with the management of toxicities/side effects of immunotherapies.

One of the specificity noted for checkpoint inhibitors is the very large number of localizations in which these therapies were tested and approved. This explains the various localizations identified among guidelines analysed, with a larger number for oldest approved indications such as melanoma (15 guidelines), lung cancer (15 guidelines) and kidney cancer (13 guidelines). It was however interesting to see that although the indication for bladder cancer was more recent, there were more guidelines identified for this therapeutic area (8 guidelines) rather than for head and neck cancer (3 guidelines) and for Hodgkin lymphoma (5 guidelines).The graph below presents the detailed distribution of clinical practice guidelines screened according to cancer localizations.

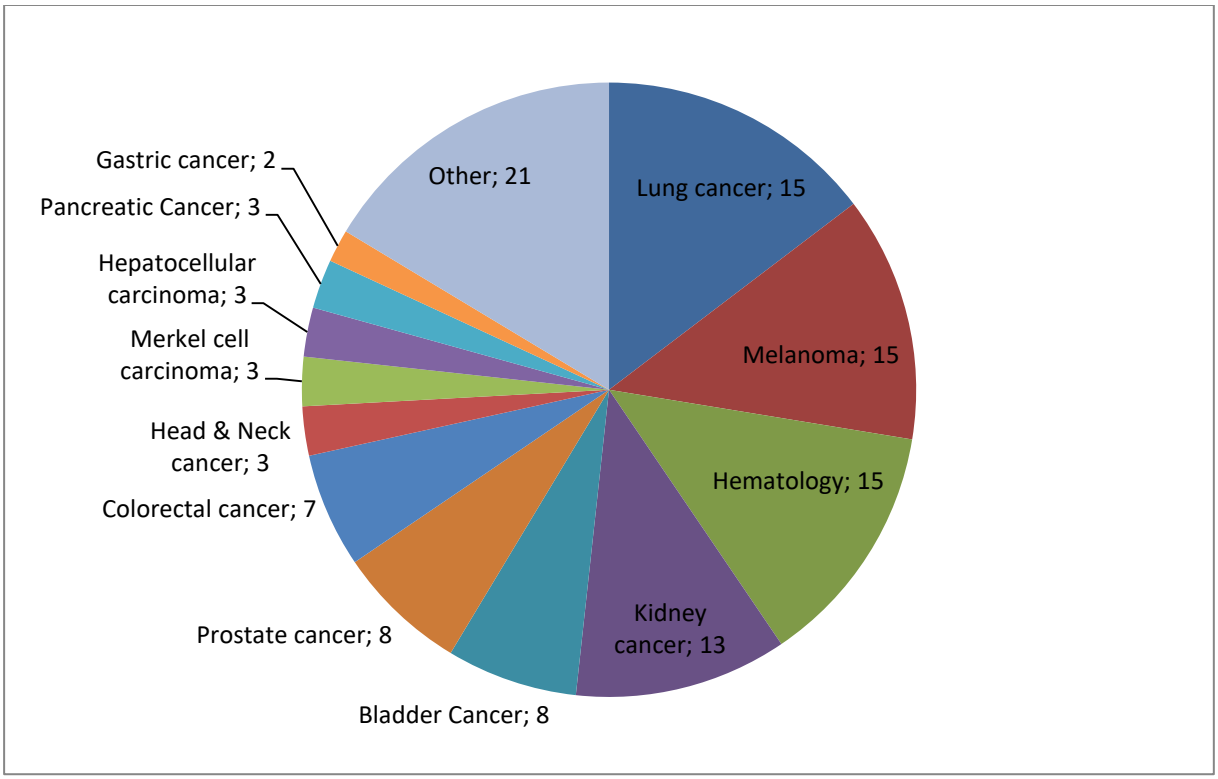


Figure 6: Distribution of the clinical practice guidelines according to the cancer localization

3.1.4 Overview of off label recommendations

69 international clinical practice guidelines including potential off-label recommendations were identified. 29 clinical practice guidelines provided recommendations considered off-label in Europe, but based on FDA approved indications. They were all from American organizations, including one collaboration between ASCO and the Cancer Care Ontario. Concerning this last collaboration, the drug and its indication was approved in the US but not in Canada. They have been excluded from the scope of the graph below.

The different categories of off-label recommendations found as well as the proportion for each of them are presented in the figure below. The detail of these recommendations will be presented at the disease level.

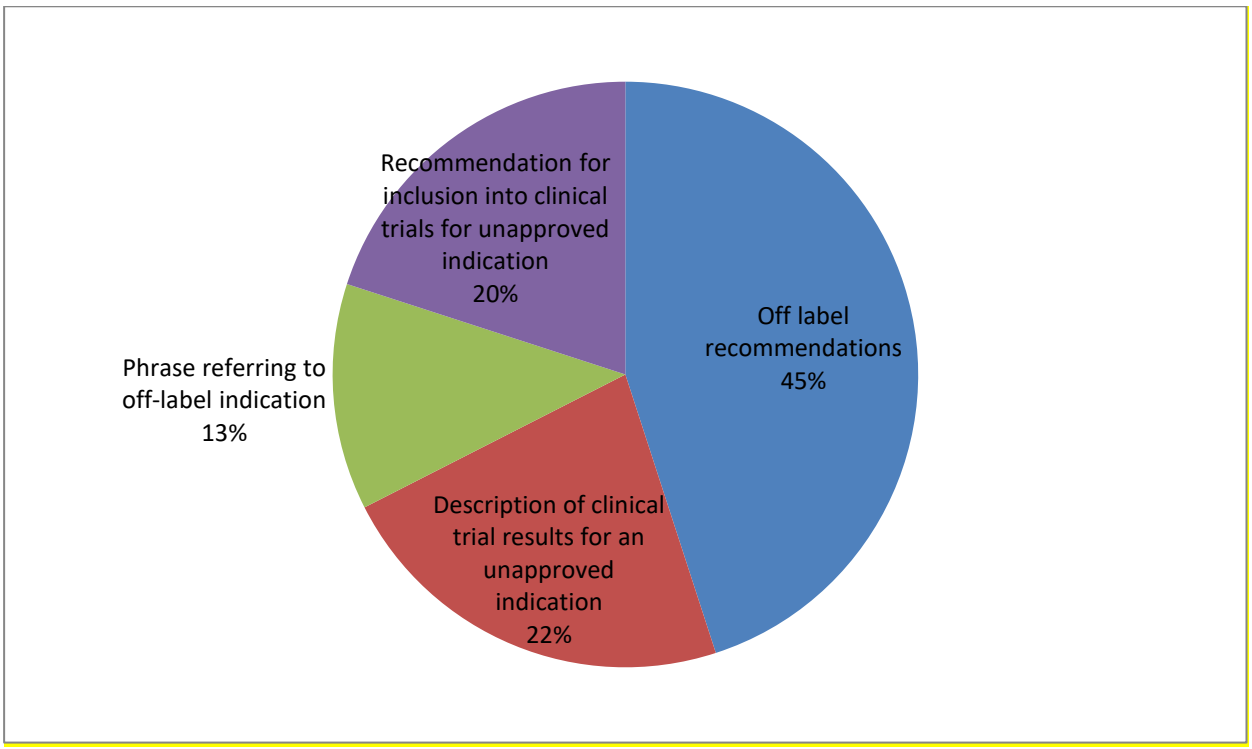


Figure 7: Repartition of categories of off-label recommendations and of recommendation for inclusion in clinical trials for an unapproved indication identified in the clinical practices guidelines

The distribution of the 40 clinical practice guidelines providing off-label recommendations depending on the category of authors is presented on the graph below.

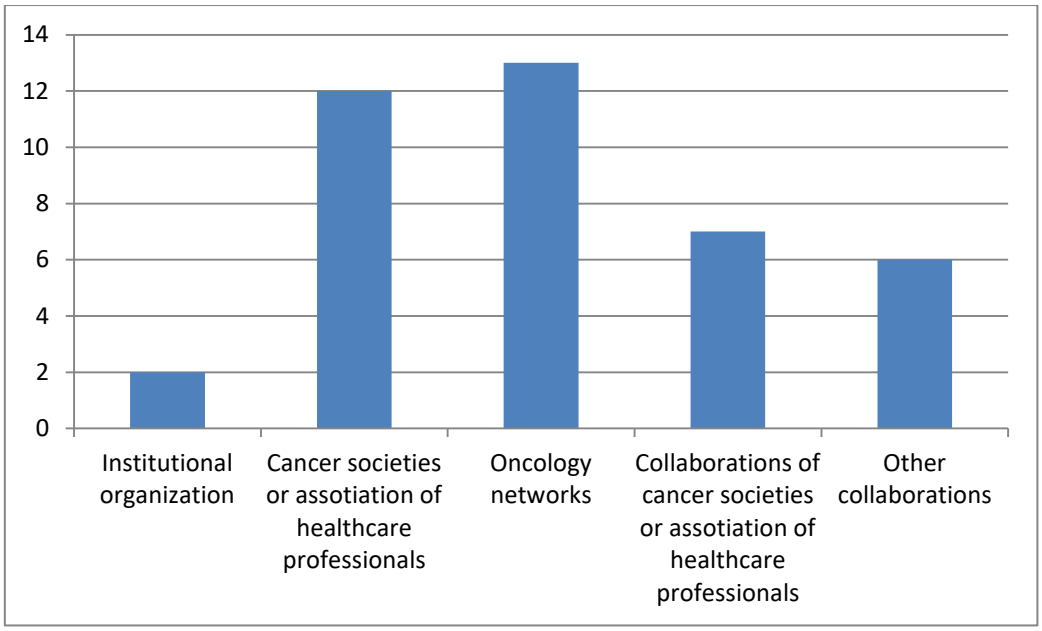


Figure 8: Distribution of off label recommendations depending on the category of authors

Among the 18 providing clear off-label recommendations:

- 11 were from the NCCN;
- 6 were from cancer societies /association of healthcare professionals from Europe (either alone or in collaboration);
- 1 from the collaboration between the Cancer Council Australia and the Melanoma institute Australia.

3.2 Innovative immunotherapy positions in the cancer treatment strategies for each localization

3.2.1 Melanoma

Current European indications of specific immunotherapies in melanoma

Table 4: Current European indications of specific immunotherapies in melanoma – January 2018

Drug	Disease	Population	Line of treatment	Date of EU AMM
ipilimumab (monotherapy)	advanced (unresectable or metastatic) melanoma	Adults	Second line	July 2011
			First line	October 2013
		Adults, and adolescents 12 years of age and older	First line	January 2018
nivolumab (monothérapie)	advanced (unresectable or metastatic) melanoma	Adults	First line	June 2015
ipilimumab + nivolumab	advanced (unresectable or metastatic) melanoma ("Relative to nivolumab monotherapy, an increase in progression-free survival (PFS) and overall survival (OS)* for the combination of nivolumab with ipilimumab is established **only in patients with low tumour PD-L1 expression**") *added in October 2017	Adults	First line	May 2016
pembrolizumab (monothérapie)	advanced (unresectable or metastatic) melanoma	Adults	First line	July 2015
Talimogene laherparepvec	unresectable melanoma that is regionally or distantly metastatic (Stage IIIB, IIIC and IVM1a) with no bone, brain, lung or other visceral disease	Adults	First line	October 2015

Scope of guidelines

8 publications regarding treatment strategies for melanoma have been retrieved with the first PubMed search. After removal of the duplicates, 6 were kept, and after checking the author's websites, we found a most updated version for 5 of them. After additional literature screening, 7 more guidelines have been identified making a total of 15 guidelines available for melanoma. Half of them were written by European organizations.

Regarding the scope of these guidelines, 7 were addressing all stages of melanoma, whereas 4 were more specific to late stage melanoma (unresectable stage III or stage IV), and 2 were dedicated to earlier stages. Two were more specific to a subtype of melanoma: one for uveal melanoma, and one for vulvar and vaginal melanoma.

One was a broader guideline as it included recommendations for oncodermatology overall, including melanoma. Another guideline from NCCN was dedicated to squamous cell skin cancer. It mentioned that clinical trials with immune checkpoint inhibitors are recommended for regional recurrence or distant metastases.

Additionally, 2 guidelines were dealing with the management of melanoma associated brain metastasis.

Place of innovative immunotherapies in the melanoma therapeutic strategy

Anti-PD-1

Most of the guidelines suggested the search for potential BRAFV600 mutation prior implementation of a systemic therapy for metastatic or unresectable melanoma.

BRAF wild patients

For the systemic therapy of metastatic or unresectable melanoma, all recent guidelines seem to agree to recommend the use of anti-PD-1 as first line option for BRAF wild patients. The levels of evidence available supporting this recommendation and grades of recommendation provided are usually high.

BRAF mutated patients

One of the difficulties identified for this subpopulation is that there is another innovative treatment option which was also recently approved: the targeted therapy anti-BRAF which is commonly used in association with an anti-MEK. The clinical development of this treatment option was performed in parallel to anti-PD-1. Therefore, there is currently no clear evidence comparing anti-BRAF/anti-MEK versus anti-PD-1 for BRAF mutated patients.

Some studies are ongoing such as the US intergroup study of dabrafenib/trametinib versus ipilimumab/nivolumab (https://clinicaltrials.gov/ct2/show/NCT02224781) and the Italian Sequential Combo Immuno and Target Therapy (SECOMBIT) Study (https://clinicaltrials.gov/ct2/show/NCT02631447).

This leads to differences regarding the place of anti-PD-1 between guidelines. Indeed, for the treatment of metastatic and/or unresectable melanoma in BRAF mutated patients, some guidelines such as INCa/SFD guidelines place anti-BRAF/anti-MEK as first line option whereas other would place these 2 treatment options at the same level and some place immunotherapies ahead for certain patients.

Furthermore, the BRAF status is not the only parameter which should be considered to determine the place of anti-PD-1. Some guidelines even provide recommendation regardless of this status, such as the guideline from EADO/EDF/EORTC which mentioned that “PD-1 checkpoint blockade either as monotherapy or in combination with CTLA-4 blockade should be considered as a good option for first-line treatment for all patients with unresectable metastatic melanoma, independently from BRAF status”. The Task Force participants from SITC also agreed that immunotherapy should be considered prior to targeted therapy in patients with good performance status regardless of BRAF mutation status.

In the NCCN guidelines, the choice depends also from the presence or not of brain metastasis.

Anti-CTLA-4

Recommendations made for ipilimumab are in agreement with the first marketing authorization obtained. However, at the time of the review, no guideline placed ipilimumab for the treatment of adolescents 12 years of age and older. This might be explained either by the recent MA or by the scope of guidelines which did not include pediatric indications.

Combination nivolumab/ipilimumab

Some controversies were observed regarding recommendations for the use of this combination option. Some guidelines recommend this combo as first line option (e.g. NCCN), other like ESMO or INCa/SFD are more balanced in their conclusions. As per ESMO guidance published in 2015 and updated in 2016, the study comparing nivolumab versus nivolumab/ipilimumab was not powered to distinguish between the efficacy of nivolumab and the ipilimumab/nivolumab combo. The final clinical implications of this study, including the question about the superiority of combined anti-PD1/CTLA-4 therapy versus sequential anti-PD1/CTLA-4 therapy, remain open until the survival data are mature (Larkin et al. 2014).

As per of INCA/SFD guidelines, anti-PD1 in monotherapy is recommended in first line, whereas the combo could be proposed in some selected patients (expert agreement).

Talimogene Laherparepvec:

This oncolytic virus has an indication for unresectable melanoma that is regionally or distantly metastatic (Stage IIIB, IIIC and IVM1a) with no bone, brain, lung or other visceral disease

For the management of unresectable stage III/IV melanoma with injectable lesions, SITC includes this oncolytic herpes virus engineered, talimogene laherparepvec (T-vec in the USA; Imlygic in Europe) as a treatment option. This decision was supported by 39% of the panel members. It is also recommended by SEOM and NCCN.

SFD/INCa: T-VEC, which has a French MA, is currently not available in France and clinical research is still ongoing to better define its place in the cancer treatment strategy.

Off-label recommendations

At the time of the guidelines review, the indication of nivolumab and pembrolizumab in the adjuvant settings for the treatment of melanoma with lymph node involvement or metastatic disease who have undergone complete resection was not approved in Europe. Therefore, 4 off-label recommendations were identified for this indication.

However 3 of them concerned American guidelines, supported by the approval from FDA. That's why, they can not be considered as off label.

The Cancer Council Australia made the following recommendations, with the precision mentioning that pembrolizumab was neither approved by the reference medicine agency in Australia - Therapeutic Goods Administration - nor funded by the Pharmaceutical Benefits Scheme (PBS) for this indication:

- "Patients with resected stage III melanoma may be considered for 12 months adjuvant treatment with pembrolizumab. [level II, grade B]".

In addition, 3 European guidelines referred to this indication providing description of ongoing clinical trials but did not properly make an off label recommendation :

In the SEOM guidelines, they mentioned ongoing trials for this indication with ipilimumab: "Adjuvant Ipilimumab at 10 mg/kg schedule has demonstrated in a phase III clinical trial (EORTC 18,071) an improvement in RFS and OS compared with placebo in resected stage III melanoma. More than 50% of patients experienced grade 3–4 adverse events, with a discontinuation rate of 32% in patients treated with ipilimumab, including 5 toxic deaths. This indication is not approved in Europe, therefore no recommendation can be made."

In their guideline for the management of metastatic or unresectable uveal melanoma, NCCN recommended the enrollment in a clinical trial as the first options, but the following treatments were also identified as potential treatment options: anti-PD-1 monotherapy, anti-CTLA-4 monotherapy; or combination of anti-PD-1 and ipilimumab. In the OncoLogik guidelines for vulvar and vaginal melanoma: treatment with anti-PD1 could be considered for metastatic and unresectable tumors if BRAF, C-Kit, NRAS are negative.

For the 2 guidelines dedicated to sub-types of melanoma, it is difficult to judge the validity of recommendations provided. These sub-populations are not excluded from the current anti-PD-1 and ipilimumab European marketing authorizations, so they are not technically considered off-label. However, it is important to specify that most of the clinical trials supporting the marketing authorization of anti-PD-1 and anti-CTLA-4 for melanoma did not include these types of melanoma, making the level of evidence available quite low to support these recommendations. For instance, it is specified in the ipilimumab summary of product characteristics that patients with ocular melanoma were not included in the following clinical trials: MDX010-20, CA184-169, CA184070 and CA184178.

Additionally, 2 guidelines were dealing with the management of melanoma associated with brain metastasis. The ANOCEF included ipilimumab as a treatment option whereas NCCN included ipilimumab + nivolumab, or pembrolizumab. Similarly to the previous example given for uveal melanoma, most of the clinical trials supporting the approval of ipilimumab, nivolumab and pembrolizumab did not include patients with active brain metastases making it hard to provide high grades for recommendations.

3.2.2 Lung cancer

Current European indications of checkpoint inhibitors in lung cancer

Table 5: Current European indications of checkpoint inhibitors in lung cancer - July 2018

Drug	Disease	Line of treatment	Date of AMM
Pembrolizumab (monotherapy)	Metastatic NSCLC in adults whose tumours express PD-L1 with a ≥ 50% tumour proportion score (TPS) with no EGFR or ALK positive tumour mutations	First Line	January 2017
Pembrolizumab (monotherapy)	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.	Second Line Patients should have received at least one prior chemotherapy regimen, and patients with EGFR or ALK positive tumour mutations should also have received targeted therapy before receiving KEYTRUDA.	July 2016 January 2017: Restriction for TPS>1%
Nivolumab (monotherapy)	Locally advanced or metastatic NSCLC	Second Line after prior chemotherapy	Oct 2015 April 2016: extension for non-squamous
Atezolizumab (monotherapy)	Locally advanced or metastatic NSCLC	Second Line after prior chemotherapy Patients with EGFR activating mutations or ALK-positive tumour mutations should also have received targeted therapy before receiving Tecentriq	September 2017

Scope of guidelines

15 clinical practice guidelines related to the treatment of lung cancer were identified with the literature review, including 7 from Europe. Most of the guidelines found were dedicated to the management of non-small cell lung cancer (N=11), including 3 specific to late stages (stage IV/metastatic) and 2 for earlier stages only (stages I to III). This corresponds to current marketing authorizations.

Additionally, 2 guidelines were identified for small-cell lung cancer, 1 for sarcomatoid lung carcinomas, and the last one included all types of lung cancers.

Finally, two guidelines were dealing with the management of lung-cancer associated with brain metastasis.

Place of innovative immunotherapies in the lung cancer therapeutic strategy

Overall, guidelines were in agreement to recommend the use of pembrolizumab as first line treatment for metastatic NSCLC in adults whose tumours express PD-L1 with a ≥ 50% tumour proportion score (TPS) with no EGFR or ALK positive tumour mutations. The level of evidence available and grades of recommendations are usually high (e.g. NCCN: category 1; ASCO: high evidence quality and strong strength of recommendation).

Similarly, guidelines usually recommended the use of either pembrolizumab (with the condition of PD-L1 expression) or nivolumab as second line option for the treatment metastatic NSCLC.

As the anti-PD-L1 atezolizumab was more recently approved (September 2017), it was less often included in the guidelines assessed.

Some key parameters influencing the position of anti-PD-1 in the therapeutic strategy were identified:

- Squamous versus non-squamous cell carcinoma: seen in older version of guidelines; mainly due to the first indication of nivolumab restricted to squamous NSCLC;
- EGFR/ALK biomarkers: due to the labeling of pembrolizumab for its indication in second line which specifies that patients should have received at least one prior chemotherapy regimen, and patients with EGFR or ALK positive tumour mutations should also have received targeted therapy before receiving KEYTRUDA;
- PD-L1 expression.

One of the difficulties identified through the example of this therapeutic area was the fast evolution of marketing authorization wording, extension of indications and the large number of clinical trials conducted, making hard for the clinical practice guidelines providers to keep a document up to date.

For instance, the number of updates performed by ESMO on their guideline covering the management of metastatic non-small-cell lung cancer is a good example to show the difficulty to maintain a document up-to-date following new MA, extension of indication and modification of the MA wording of checkpoint inhibitors in this therapeutic field:

- Prior arrival of checkpoint inhibitors on the market

⇨ Version from 2014

- October 2015: First marketing authorization: nivolumab approved in Europe in October 2015 for the treatment of locally advanced or metastatic squamous non-small cell lung cancer (NSCLC) after prior chemotherapy in adults
- April 2016: extension of indication for nivolumab to non-squamous NSCLC.
- July 2016: first approval of pembrolizumab for second line treatment of NSCLC. (Patients should have received at least one prior chemotherapy regimen, and patients with EGFR or ALK positive tumour mutations should also have received targeted therapy before receiving KEYTRUDA.)

⇨ One version published in August 2016 including nivolumab and pembrolizumab as second line option for NSCLC

The level of evidence as well as the grade of recommendation depends on the PD-L1 expression: "Based on the KEYNOTE-010 trial [96], pembrolizumab is another immunotherapy option in second-line but also in third-line therapy in patients with NSCC expressing [I, A; ESMO-MCBS v1.0 score: 3 if PD-L1 <1%; 5 if PDL1>50%]."

- January 2017: modification of the MA wording for pembrolizumab second line to specify the score of PD-L1 expression in tumours cells (≥ 1% TPS) + new indication as first line

⇨ E-updated published in June 2017 to integrate these changes

- September 2017: new anti-PD-L1 approved for NSCLC: atezolizumab

⇨ New version published in October 2018

- 31 January 2019: The CHMP adopted two new indications:

  KEYTRUDA, in combination with carboplatin and either paclitaxel or nab-paclitaxel, is indicated for the first-line treatment of metastatic squamous non-small cell lung cancer (NSCLC) in adults.

  Tecentriq, in combination with bevacizumab, paclitaxel and carboplatin, is indicated for the first-line treatment of adult patients with metastatic non-squamous non‑small cell lung cancer (NSCLC). In patients with EGFR mutant or ALK-positive NSCLC, Tecentriq, in combination with bevacizumab, paclitaxel and carboplatin, is indicated only after failure of appropriate targeted therapies (see section 5.1).

⇨ ESMO publication release on their website to inform the medical community; not yet implemented within the related clinical practice guideline

Off-label recommendations

ASCO and ESMO mentioned ongoing clinical trials in adjuvant settings for the earlier stages of NSCLC.

Regarding off-label recommendations, most of them were associated with differences between USA and European marketing authorizations. For instance, the use of immunotherapies in association with chemotherapy for NSCLC has been approved in 2018 the United States. The first European MAs for such association are from January 2019 (see above example with pembrolizumab and atezolizumab). Durvalumab has been approved back in May 2017 in the USA, so it is quite well integrated in American guidelines whereas it was only recently approved in September 2018 in Europe (most of the guidelines assessed were published before).

Off-label recommendation was identified for the management of small cell lung cancer: NCCN recommended nivolumab and nivolumab + ipilimumab as subsequent treatment options for patients with small cell lung cancer who have relapsed 6 months or less after primary therapy, in the version published in January 2018; whereas nivolumab was approved by the FDA for this indication only in April 2018.

3.2.3 Renal cell carcinoma

Current European indications of checkpoint inhibitors in renal cell carcinoma

Table 6: Current European indications of checkpoint inhibitors in renal cell carcinoma – January 2019

Drug	Disease	Line of treatment	Date of EU AMM
Nivolumab (monotherapy)	Advanced renal cell carcinoma	Second or third line (after prior therapy in adults)	April 2016
Nivolumab + ipilumumab	Advanced renal cell carcinoma	First-line treatment of adult patients with intermediate/poor-risk advanced renal cell carcinoma	January 2019

Scope of guidelines

13 guidelines were identified for kidney cancer, including 6 from European organizations. Three of them were dedicated to advanced/ metastatic stages whereas all the other addressed all stages. Half of them focused on the renal cell carcinoma whereas other included recommendations for all types of renal cancers. One consensus statement from the international society of geriatric oncology was dedicated to elderly patients.

Place of innovative immunotherapies in the renal cell carcinoma therapeutic strategy

For renal cell carcinoma, all recommendations are in line with the approved European therapeutic indication of nivolumab from 2016.

Off-label recommendations

Off-label recommendations identified were triggered by the FDA approval of nivolumab + ipilimumab combination as first-line treatment for patients with intermediate- and poor-risk advanced renal cell carcinoma in April 2018.

Indeed, both NCCN and the European association of urology recommend this association in treatment-naïve patients with clear-cell metastatic RCC of intermediate and poor prognostic risk with a high grade of recommendation (strong for EAU, cat 1 for NCCN).

They also recommend ipilimumab plus nivolumab to treatment-naïve patients with favorable-risk group metastatic clear cell RCC but the grade of recommendation is lower (weak for EAU, cat 2B for NCCN.

3.2.4 Bladder cancer

Current European indications of checkpoint inhibitors in bladder cancer

Table 7: Current European indications of checkpoint inhibitors in bladder cancer - July 2018

Drug	Disease	Line of treatment	Date of EU AMM
Nivolumab (monotherapy)	locally advanced unresectable or metastatic urothelial carcinoma	Second line (after failure of prior platinum-containing therapy)	June 2017
Pembrolizumab (monotherapy)	locally advanced or metastatic urothelial carcinoma	Second line (after platinum-containing chemotherapy)	August 2017
Pembrolizumab (monotherapy)	locally advanced or metastatic urothelial carcinoma	First line for adults who are not eligible for cisplatin-containing chemotherapy	August 2017
Atezolizumab (monotherapy)	locally advanced or metastatic urothelial carcinoma	Second line (after platinum-containing chemotherapy)	September 2017
Atezolizumab (monotherapy)	locally advanced or metastatic urothelial carcinoma	First line for adults who are considered cisplatin ineligible, and whose tumours have a PD-L1 expression ≥ 5%	September 2017

Scope of guidelines

8 guidelines were identified in this therapeutic area. Only three of them were from a European organization: one from the European Association of Urology, one from NICE and the third from the cancerology committee of the French association of urology. However, this last guideline was published in 2016, prior the approval of checkpoint inhibitors in Europe for this indication. All the other guidelines were from the United States.

Four of the 8 guidelines dealt with bladder cancer in general whereas 2 were focusing on late stages (metastatic/muscle invasive bladder cancer) and 2 on earlier stages.

Place of innovative immunotherapies in bladder cancer treatment strategies

One of the main factors influencing the position of checkpoint inhibitors in the therapeutic strategy is the PD-L1 expression. This is especially the case for atezolizumab for which the marketing authorization specifies that atezolizumab as 1st line treatment can be prescribed only in patients whose tumours express PD-L1 ≥ 5%.

NICE does not recommended Nivolumab, within its marketing authorization, as an option for treating locally advanced unresectable or metastatic urothelial carcinoma in adults who have had platinum-containing therapy.

MSI-H: In the consensus statement written by the Society for immunotherapy of cancer consensus on “Immunotherapy for the treatment of bladder cancer”, they do mention that pembrolizumab is an appropriate choice of treatment in any patient whose tumor has the MSI-H biomarker and whose disease had progressed following prior treatment, with no satisfactory alternative treatment options.

The guidelines from AUA/SUO (2016), from AUA/ASCO/ASTR/SUO (2017) and from CC-AFU (2016) recommend the use of anti-PD-1 and anti-PD-L1 only through clinical trials. This could be explained by the publication before the first approval date.

Off-label recommendations

Off-label recommendations mainly depend on differences between European and American indication. For instance, NCCN recommends pembrolizumab as the preferred option for subsequent systemic –therapy for locally advanced or metastatic disease (stage IV, post platinium) [cat 1]. Alternative preferred regimen suggested by the NCCN included nivolumab and atezolizumab, which are both approved in Europe, but it also included durvalumab and avelumab, which are not approved in Europe. NCI and SITC also provide durvalumab and avelumab as option for this indication, but the level of evidence assessed by NICE is weaker. SITC specify that pembrolizumab is the only agent with the strongest level of evidence.

NCCN recommends pembrolizumab as first line option for patients whose tumors express PD-L1 (CPS>10), regardless if they are eligible for platinium chemotherapy is off label. The European authorization for pembrolizumab as first line treatment is only for patients uneligible to cisplatin-containing chemotherapy.

3.2.5 Head and neck/Upper AeroDigestive Tract Cancer

Current European indications of checkpoint inhibitors in head and neck cancer

Table 8: Current European indications of checkpoint inhibitors in head and neck cancer - Sept 2018

Drug	Disease	Line of treatment	Date of EU AMM
Nivolumab (monotherapy)	progressing squamous cell cancer of the head and neck	Second line (after platinum-based therapy)	April 2017
Pembrolizumab (monotherapy)	recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) in adults whose tumours express PD-L1 with a ≥ 50% TPS	Second line (progressing on or after platinum-containing chemotherapy)	September 2018

Scope of guidelines

Only 3 guidelines were identified for this therapeutic area: one from NCCN, one from the Spanish society of medical oncology (SEOM) and one from the NICE. This could be explained by the lower incidence of this cancer, and thus lower number of societies specified in this field.

Additionally, 2 guidelines written by ESMO, both in collaboration with the EHNS and ESTRO were identified. However they were not included in the table as published prior 2011. The Clinical Practice Guidelines for diagnosis, treatment and follow-up for squamous cell carcinoma of the head and neck, co-written by EHNS-ESMO-ESTRO was indeed published in 2010. They did not include any recommendation on innovative immunotherapies. The second one concerned nasopharyngeal cancer, but no innovative immunotherapies were referred as treatment options neither.

Place of innovative immunotherapies in head and neck cancers treatment strategies

The three guidelines identified provided recommendations in line with the European marketing authorization of nivolumab with the highest grades of recommendations.

Off-label recommendations

SEOM provided off-label recommendation for pembrolizumab. Indeed, at the time of publication of these guidelines in 2017, pembrolizumab was not yet approved in Europe for this indication. It was highlighted that the level of evidence available was lower than for nivolumab, but the restriction of the European MA to patients whose tumours express PD-L1 ≥ 50% TPS was not anticipated.

Additionally, NCCN also recommended the use of pembrolizumab for the treatment of progressing squamous cell cancer of the head and neck, but this was supported by the American MA.

3.2.6 Prostate cancer

Current European indications of checkpoint inhibitors in prostate cancer

There is no current approved marketing authorization in Europe for innovative immunotherapies for the treatment of prostate cancer.

Scope of guidelines

Some guidelines were retrieved from the literature search as they were placing the immunotherapy Sipuleucel-T (Provenge® in Europe) in the prostate cancer treatment strategy. Indeed, this therapy was granted marketing authorization in Europe in September 2013 for the treatment of castration-resistant metastatic prostate cancer. Provenge® is a type of advanced therapy medicine called a somatic cell therapy product.

However, as per the European Medicines Agency public statement published on 11 May 2015: “On 6 May 2015, the European Commission withdrew the marketing authorisation for Provenge (autologous peripheral blood mononuclear cells activated with PAP-GM-CSF (sipuleucel-T)) in the European Union (EU). The withdrawal was at the request of the marketing authorisation holder, Dendreon UK Ltd, which notified the European Commission of its decision to permanently discontinue the marketing of the product for commercial reasons.”

In total, 8 guidelines were found for prostate cancer, including half of them specific to castration-resistant prostate cancer.

Place of innovative immunotherapies in prostate cancer treatment strategies

As sipuleucel T is still on the market in the United States, we still retrieve recent and actual guidelines positioning this immunotherapy in the prostate cancer treatment strategy like ASCO/Cancer Care Ontario (Sept 2014), SITC (Dec 2016), NCCN (August 2018) and the American Urology Association (lastly updated in 2018).

Four European guidelines place sipuleucel-T as a treatment option for castration-resistant metastatic prostate cancer. However, the ESMO guidelines were published in May 2015, at the same time of the EU withdrawal. The guideline from the Spanish Oncology Genitourinary

Group was published in 2015, but the clinical data were reviewed up to September 2014. The publication from the European Expert Consensus Panel was published in April 2014.

Only one recent publication from the French ccAFU was found in which the results of the clinical trials with sipuleucel T as well as with ipilimumab are described. They also specify that Sipuleucel T is currently not available in Europe.

Off-label recommendations

The NCCN recommends Pembrolizumab only for MSI-H or dMMR tumors, as subsequent systemic therapy for patients who have progressed through at least one line of systemic therapy for M1 castration-resistant metastatic prostate cancer [cat 2B]. This is currently considered off-label in Europe.

3.2.7 Hematologic cancers

Current European indications of specific immunotherapies in hematologic cancers

Table 9: Current European indications of checkpoint inhibitors for Hodgkin lymphoma – July 2018

Drug	Disease	Line of treatment	Date of EU AMM
Nivolumab (monotherapy)	Relapsed of refractory classical Hodgkin lymphoma	Third line After autologous stem cell transplant (ASCT) and treatment with brentuximab vedotin	November 2016
Pembrolizumab (monotherapy)	Relapsed of refractory classical Hodgkin lymphoma	Third line For adult patients who have failed autologous stem cell transplant (ASCT) and brentuximab vedotin (BV), or who are transplant-ineligible and have failed BV	May 2017

Table 10: Current European indications of CAR-T cells for acute lymphoblastic leukemia - August 2018

Drug	Population	Disease	Line of treatment	Date of EU AMM
Tisagenlecleucel (monotherapy)	Paediatric and young adult patients up to 25 years of age	B-cell acute lymphoblastic leukaemia (ALL) that is refractory	In relapse post-transplant or in second or later relapse	August 2018

Table 11: Current European indications of CAR-T cells for lymphomas

Drug	Disease	Line of treatment	Date of EU AMM
Tisagenlecleucel (monotherapy)	Adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL)	After two or more lines of systemic therapy	August 2018
Axicabtagene ciloleucel (monotherapy)	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	August 2018

Scope of guidelines

15 guidelines were identified for hematologic cancers covering the following diseases:

- Hodgkin lymphoma: N=5
- Lymphomas: N=4, including 2 NCCN guidelines with 1 specific to B-cell lymphomas and the other one specific to T-cell lymphomas
- Acute lymphoblastic leukemia: N=4 (to be noted: documentation from NCI was split : one doc for adults, the other for the pediatric population)
- Chronic Lymphocytic Leukemia: N=2

Place of innovative immunotherapies in hematologic cancer treatment strategies

Checkpoint inhibitors

Regarding the 2 checkpoint inhibitors for the treatment of Hodgkin lymphoma, NCCN, ESMO, the French and the 2 Canadian guidelines recommend their use within the marketing authorization. However, it was highlighted in most of the guidelines that the level of evidence supporting these recommendations was quite low (single-arm, phase II, not controlled trials); thus, grades of recommendations observed were moderate as well (ESMO: III/B; NCCN: category 2A).

In the clinical trials supporting the marketing authorization of nivolumab and pembrolizumab (as well as above recommendations), anti-PD-1 were not directly compared to another treatment. Indeed, there is no current standard of care in the population targeted by these 2 indications. The ESMO and NCCN recommendations offered options with chemotherapies which did not have a marketing authorization (gemcitabine, bendamustine, lenalidomide or everolimus). Thus, it is hard to determine what would be the best comparator and to define the best place for anti-PD-1 within the Hodgkin lymphoma therapeutic strategy.

The position compared to brentuximab vedotin is also hard to assess. For instance, the American marketing authorization does not specify the need for patients to have received this therapy prior treatment with checkpoint inhibitors.

The NICE recommendations are in agreement with the 4 other guidelines identified for the management of Hodgkin lymphoma with nivolumab. However, they are more restrictive than the marketing authorization for pembrolizumab. Indeed, they do not recommend pembrolizumab for treating relapsed or refractory classical Hodgkin lymphoma in adults who have had autologous stem cell transplant and brentuximab vedotin. Pembrolizumab is recommended for use within the Cancer Drugs Fund only as an option for treating relapsed or refractory classical Hodgkin lymphoma in adults who have had brentuximab vedotin and cannot have autologous stem cell transplant. Additionally, they limit their recommendation for a length of treatment up to 2 years maximum.

Other therapies identified

Some guidelines were retrieved because of the immunotherapy “Rituximab” but these guidelines were not included in the table as rituximab is not considered as an innovative immunotherapy.

Additionally, recommendations for the use of blinatumomab were identified in the guidelines screening. This bispecific anti-CD3/CD19 monoclonal antibody was not included in the main focus of the WP as the mechanism of action was not considered to be innovative.

The first European indication of blinatumomab, obtained in November 2015 was the following: “BLINCYTO is indicated for the treatment of adults with Philadelphia chromosome negative relapsed or refractory B-precursor acute lymphoblastic leukaemia (ALL).” On 26 July 2018, the European Medicines Agency (EMA) provided a positive opinion for the extension of indication to paediatric patients aged 1 year or older with Philadelphia chromosome negative, CD19-positive B-cell precursor acute lymphoblastic leukaemia which is refractory or in relapse after receiving at least two prior therapies or in relapse after receiving prior allogeneic hematopoietic stem cell transplantation.

Off-label recommendations

Checkpoint inhibitors:

For the management of Hodgkin lymphoma, the NCCN also recommend checkpoint inhibitors as an option for patients who would not have received brentuximab vedotin. This is supported by the FDA approved marketing authorization of pembrolizumab which does not specify the previous treatment that patients should have received (pembrolizumab is indicated for classical Hodgkin lymphoma "for the treatment of adult and pediatric patients with refractory cHL, or who have relapsed after 3 or more prior lines of therapy"). To be noted that the FDA indication of nivolumab is a little bit more specific: "adult patients with classical Hodgkin lymphoma that has relapsed or progressed after: - autologous hematopoietic stem cell transplantation (HSCT) and brentuximab vedotin, or - 3 or more lines of systemic therapy that includes autologous HSCT".

In the United States, pembrolizumab is also approved for the treatment of refractory or relapsed primary mediastinal large b-cell lymphoma since June 2018. This lead to recommendations in NCCN guidelines for this indication. Additionnally, NCCN recommended the following for chronic lymphocytic leukemia and richter's transformation / diffuse large B-cell lymphoma: clinical trials are preferred, but if no other chemoimmunotherapy can be received, the following options can be considered: nivolumab + ibrutinib [cat 2B] or pembrolizumab + ibrutinib [cat 2B].

Finally, the following recommendations concerning T-cell lymphomas are provided in the NCCN guidelines:

- Extranodal NK/T-cell lymphoma, nasal type - relapsed/refractory disease: pembrolizumab recommended as a treatment option in the absence of a clinical trial.
- Systemic therapies for Mycosis Fungoides/Sezary Syndrome: pembrolizumab is a possible therapy [cat 2B]

CAR-T cells

Due to the very recent approval of CAR-T cells in Europe, only American clinical guidelines were positioning these therapies as treatment options for refractory B-cell acute lymphoblastic leukaemia (Kymriah®) and for relapsed or refractory large B-cell lymphoma (Kymriah® and Yescarta®).

Ongoing clinical trials with these gene and cell therapies were referred into the ESMO guidelines.

3.2.8 Merkel cell carcinoma

Current European indications of checkpoint inhibitors for Merkel cell carcinoma

Table 12: Current European indications of checkpoint inhibitors for Merkel cell carcinoma - July 2018

Drug	Disease	Line of treatment	Date of EU AMM
Avelumab (monotherapy)	metastatic Merkel cell carcinoma	Not specified	Sept 2017

Scope of guidelines

3 documents were identified for the management of Merkel cell carcinoma: one from NCCN, one from the NICE, and one consensus statement from a collaboration between the following European organizations: European Dermatology Forum (EDF), European Association of Dermato-Oncology (EADO) and European Organization for Research and Treatment of Cancer (EORTC) from 2015.

Place of innovative immunotherapies in Merkel cell carcinoma treatment strategies

Even though the marketing authorization of avelumab does not specify the line of treatment for this therapy, the NICE restricted their recommendation as a therapeutic option only for patients who would have received 1 or more lines of chemotherapy for metastatic disease.

NCCN recommends avelumab within its marketing authorization.

Off-label recommendations

NCCN also recommend pembrolizumab and nivolumab in addition to avelumab, as recommended systemic therapy options for treatment of disseminated disease [cat 2A]. This is not supported by an FDA indication.

The European consensus was published in 2015, prior the approval of any immunotherapy for this therapeutic indication. It was however already referring to ongoing clinical trials with anti-PD1/PD-L1 and anti-CTLA-4.

3.2.9 Colorectal cancer

Current European indications of specific immunotherapies for colorectal cancer

As of March 2019, there is no current approved indication of innovative immunotherapies for colorectal cancer in Europe.

However, in the United States, pembrolizumab has been approved since May 2017 for the treatment of adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient

- solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options or
- colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.

Additionally, since August 2017, nivolumab has been approved since in for adult and pediatric (12 years and older) patients with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.

The FDA label specifies that “this indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.”

More recently, in July 2018, the FDA granted accelerated approval to ipilimumab for use in combination with nivolumab for this same indication (treatment of patients 12 years of age and older with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer (mCRC) that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.)

Scope of guidelines

7 guidelines were identified for the management of colorectal cancer, including 4 from European organizations. Concerning the scope covered by the guidelines: 3 were dedicated to all stages, whereas 3 were focusing on metastatic colorectal and 1 on earlier stages. The NCCN has chosen to divide the recommendations into 2 different guidelines: one for rectal cancer, and the other one for colon cancer.

Place of innovative immunotherapies in colorectal cancer treatment strategies

In the two NCCN guidelines, pembrolizumab, nivolumab, or nivolumab in combination with ipilimumab are recommended within their marketing authorization as subsequent-line treatment options in patients with metastatic MMR-deficient colon and rectal cancer. There is thus a strong influence of biomarker expression to determine the place of checkpoint inhibitors for this cancer localization.

Off-label recommendations

For metastatic colorectal cancer, the clinical practice guidelines from the French national thesaurus of digestive oncology (TNCD) recommended that treatment with anti-PD-1 or anti-PD-L1 should be considered ideally in a therapeutic trial pending the marketing authorization of immunotherapy in this situation (expert agreement). For non-metastatic colorectal cancer, the TNCD also mentioned that the determination of the MSI status can orientate towards a treatment with immunotherapy. TNCD does not make properly an off label recommendation but recognizes the relevance of treating in clinical trials patients with anti-PD1 in a specific unauthorized indication.

ESMO, in their consensus guidelines for the management of patients with metastatic colorectal cancer, as well as in their adapted pan-Asia consensus guidelines with the Japanese society of medical oncology also mentioned that the MSI testing has a strong predictive value for the use of immune check-point inhibitors in the treatment of patients with mCRC [II, B].

Finally, the Cancer Council Australian also included a practice point in their guidelines mentioning that “MSI testing may be a predictive marker for the use of immune checkpoint inhibitors in the treatment of patients with metastatic colorectal cancer.”

It is important to highlight at this point that, even though there was no approved indication of checkpoint inhibitors for colorectal cancer in Europe or Australia, all guidelines assessed included at least a reference to these therapies.

3.2.10 Other off-label indications

MSI-H tumours

Following the approval of pembrolizumab by the FDA for histological tumors presenting the biomarker MSI-H / dMMR, the NCCN has updated many guidelines by adding pembrolizumab as treatment options if the tumors presented this biomarker. The table below presents all localizations for which NCCN has placed pembrolizumab as a treatment option for MSI-H tumors:

Table 13: NCCN recommendation linked with MSI-H tumours by cancer localization

Cancer localization	NCCN recommendation linked with MSI-H tumours August 2018
Bone cancer	Pembrolizumab is a systemic treatment option for adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options. NCCN recommends this treatment for patients with MSI-H/dMMR chondrosarcomas, Ewing sarcomas and osteosarcomas [cat 2A]. NCCN does not recommend this systematic treatment for GCTB since it is not technically a malignant tumor, not does it recommend pembrolizumab for chordomas due to limited evidence for the presence of MSI in this tumor type.
Cervical cancer	Pembrolizumab is recommended for recurrent or metastatic disease as second line therapy for PD-L1-positive or MSI-H/dMMR tumors [cat 2A]
Esophageal cancer	pembrolizumab as preferred regimen for second-line or susbsequent therapy for MSI-H or dMMR tumors [cat 2A]
Gastric cancer	pembrolizumab as possible second-line or susbsequent therapy for MSI-H or dMMR tumors [cat 2A]
Gallbladder cancer	treatment options for unresectable or metastatic biliary tract cancers include pembrolizumab for patients with MSI-H/dMMR tumors [cat 2A]
Neuroendocrine and Adrenal tumours	Pembrolizumab should be considered for dMMR or MSI-H unresectable/metastatic adrenocortical tumors that have progressed following prior treatment and have no satisfactory alternative treatment options
Ovarian cancer (including fallopian tube cancer & primary peritoneal cancer)	Acceptable recurrence therapies for epithelial (including LCOH)/Fallopian Tube/Primary Peritoneal cancer; for MSI-H or dMMR solid tumors: pembrolizumab [2A]
Pancreatic adenocarcinoma	Second-line therapy for locally advanced/metastatic disease; only for MSI-H or dMMR tumors: pembrolizumab
Penile cancer	Subsequent-line: pembrolizumab, if unresectable or metastatic, MSI-H or dMMR tumor that has progressed following prior treatment and no satisfactory alternative treatment option. Clinical trials preferred.
Testicular cancer	Third-line therapy: clinical trials preferred. Alternative options include microsatellite instability testing (if disease progresses after high-doses chemotherapy or third line therapy). Patients with MSI-H tumors may be candidates for pembrolizumab.
Endometrial cancer	Systemic therapy options for recurrent, metastatic or high-risk disease (participation in CT strongly recommended): pembrolizumab for MSI-H ordMMR tumors
Vulvar cancer	Chemotherapy for advanced, recurrent/metastatic disease: pembrolizumab: recommended as second-line therapy for PD-L1 positive (CPS>1) or MSI-H/dMMR tumors

In addition to the NCCN, other organizations have also included information regarding this biomarker

- TNCD for stomach cancer: description of CT results
- ASCO for pancreatic cancer: “PD-1 immune checkpoint inhibitor pembrolizumab is recommended as second-line therapy for patients who have tested

positive for dMMR or MSI-H (Type: evidence-based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate). Routine testing for dMMR or MSI-H is recommended, using IHC, PCR, or NGS for patients who are considered to be candidates for checkpoint inhibitor therapy (Type: informal consensus, benefits outweigh harms; Evidence quality: low; Strength of recommendation: moderate)."

- ESMO: For advanced breast cancer patient presenting with a tumour with MSI-H/MMR deficiency, treatment with an anti-PD-1 agent is a possible consideration (LoE/GoR: Expert opinion/C ; Consensus: Yes: 29%, Abstain: 24% ; Insufficient data: 47%)

Pancreatic cancer

TNCD does not make off label recommendation but supports direction towards clinical trials.

Hepatocellular cancer

TNCD: description of clinical trial results.

EASL (European Association for the study of the Liver): Based on uncontrolled but promising data, immune therapy with nivolumab has received FDA approval in second-line treatment, pending phase III data for conventional approval. At present, the data are not mature enough to give a clear recommendation (evidence moderate; recommendation weak).

AASLD (American Association for the study of Liver Diseases): Upon radiological progression to sorafenib, regorafenib and nivolumab should be considered as second-line options.

Gastric cancer

ESMO: description of clinical trial results.

Anal cancer

Nivolumab and pembrolizumab were recommended as subsequent therapy/second-line treatment of metastatic anal cancer by NCCN [cat 2A]. However, microsatellite instability (MSI)/mismatch repair (MMR) testing is not recommended as MSI was judged to be uncommon in anal cancer.

Malignant pleural mesothelioma:

NCCN recommends the following subsequent immunotherapy options for patients with malignant pleural mesotheliom:

Pembrolizumab [cat 2A]

Nivolumab, with or without ipilimumab [cat 2B]

ESMO also mentioned: “Second line therapy for mesothelioma: Immunotherapy targeting CTLA4 with tremelimumab is under evaluation in a large global phase III trial [NCT01843374]. Recent data suggest that the PDL1, a putative biomarker for PD1/PDL1 therapy, is significantly expressed in mesotheliomas, particularly the sarcomatoid subtype. In the absence of standard second-line or further-line therapy, it is recommended that patients are enrolled into clinical trials.”

PD-L1 positive esophageal and adenocarcinoma of the esophagogastric junction

NCCN recommend pembrolizumab for third line or subsequent therapy for PD-L1 positive esophageal and adenocarcinoma of the esophagogastric junction [cat 2A].

Chordomas

Referential Chordomas 2018 from l'ANOCEF and French sarcoma group : anti-PD-L1 could be discussed as treatment options for recurrent or metastatic chordomas.

Vulvar squamous cell carcinoma

NCCN: pembrolizumab was recommended as second-line therapy for PD-L1 positive (CPS>1) or MSI-H/dMMR tumors for recurrent/metastatic disease.

3.3 Challenges to explore further notably with the questionnaire

- Missing data leads to uncertainty of recommendations

Recommendations involving the length of treatment and the best dosing schedule were not often provided. It was however often highlighted in clinical practice guidelines that these parameters remain yet to be further characterized with more robust evidence.

In the context of missing data, it can be hard to define the best place for an innovative therapy within the cancer treatment strategy. This is the example for BRAF-mutated patients with unresectable or metastatic melanoma who could receive either anti-BRAF/anti-MEK or anti-PD-1. There is currently no clear evidence comparing the efficacy and safety of these 2 treatment options as they were developed in parallel. It is thus hard to define whether one treatment option should be prefer over the other one. This leads to differences between guidelines regarding the position of these innovative immunotherapies.

- Difficulties to keep a clinical practice guideline up to date in a very fast evolving field

Timelines for production and updates differed quite a lot between organizations. For instance, the NCCN has updated several times a year its guidelines for some specific localizations.

In the ESMO Standard Operating Procedure (SOP) related to the instructions for authors and templates for standard clinical practice guidelines, it is specified that “in the case of a significant breakthrough that necessitates rapid communication as Guideline content or in the case of a new EMA indication bearing an MCBS score, the relevant Subject Editor will coordinate with the guideline authors and produce an eUpdate. This will be posted in the ESMO Guidelines Website and published at Annals of Oncology every 4-6 months, grouped together with all eUpdates produced.”

However, the organizations in charge of providing guidelines do not always specify the frequency of updates performed.

- Lack of visibility

We noted a lack of visibility of existing national/regional clinical practice guidelines on PubMed. Indeed, only 20 out of the 120 guidelines selected were identified though the initial PubMed search.

This lead to the inclusion of questions related to the best ways to communicate on the release of a new or of an updated version of a guideline in the second questionnaire in order to obtain experts feedback.

- Methodology

Some steps are essential and followed by all such as the review of existing literature; deep analysis of clinical trials results.

Some organizations have very detailed SOPs for methodology which are publicly available on their website which make it clear to understand the method applied. Sometimes, especially for consensus statement, the methodology applied is less detailed.

For instance, differences were noted regarding the management of conflict of interests. Some organizations just list the potential conflicts existing whereas other would restrict the participation of experts only if they do not have any potential conflict of interests.

This could partly be explained by the fact that the review of literature included both clinical practice guidelines and consensus statements for which the methodology is generally lighten.

- Different levels of off-label recommendations

Different levels of recommendations for off-label indications are observed into clinical practice documents. This is why some questions related to the acceptability of off-label recommendations in clinical practice guidelines were added within the questionnaire.

3.4 Results from the questionnaire addressed to iPAAC partners

3.4.1 Completion of the questionnaire

The questionnaire was launched on 16 October 2018 and the last answer was provided on 27 November 2018. The questionnaire was organized into 3 different sections:

1. Organizations writing/providing clinical practice guidelines in European countries;
2. The availability and accessibility of innovative immunotherapies in European countries, especially in terms of reimbursement;
3. Existing programs enabling early access to innovation therapies against cancer for unapproved indication

Only results related to the first section are presented in this document. The results related to the sections 2 and 3 of the questionnaire are presented in the second iPAAC WP9 deliverable entitled “Reference frameworks linked with the access to innovative therapies”.

The questionnaire was addressed to the 24 iPAAC associated partners with the addition of 2 countries which are usually represented at the iPAAC Governmental Board by ministry representatives: Austria and the Netherlands. It was also addressed to UK.

In total, we received an answer from 23 out of the 27 countries contacted. The answers were missing for 3 iPAAC countries: Bulgaria, Poland and Romania.

For some countries, several persons replied to the questionnaire. We combined the answers from these different persons for all countries, except for Spain where the results were quite different due to regional differences identified.

A total of 24 answers were included in the analysis. The graph below represents countries which provided a reply in green and those who did not in red.

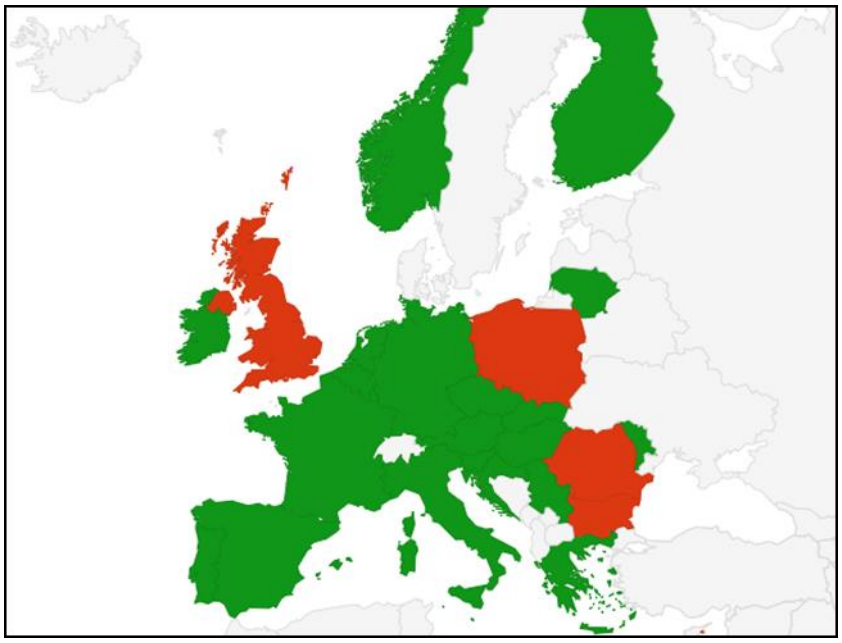
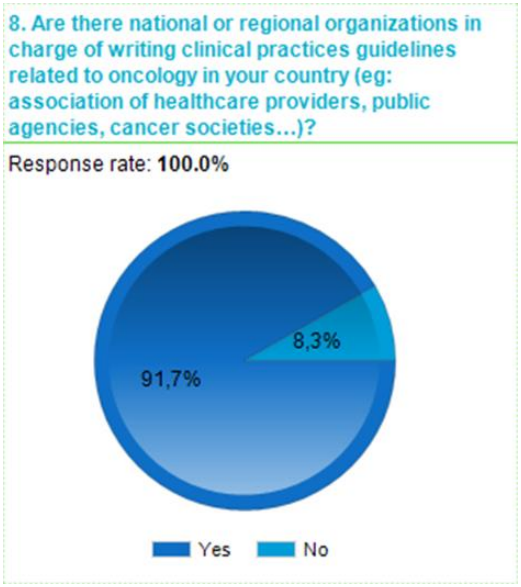


Figure 9: Completion of the questionnaire addressed to iPAAC partners

3.4.2 National and or Regional organizations in charge of writing clinical practice guidelines

Most of the countries participating in the questionnaire have at least one national or regional organization in charge of writing clinical practices guidelines related to oncology.



Countries where there was no organizations identified were asked to specify clinical practice guidelines and reference documents used by healthcare professionals working in the oncology field in their country. In Malta for instance, where they do not have a system in place for writing guidelines, they specified that “Guidelines and protocols in the English

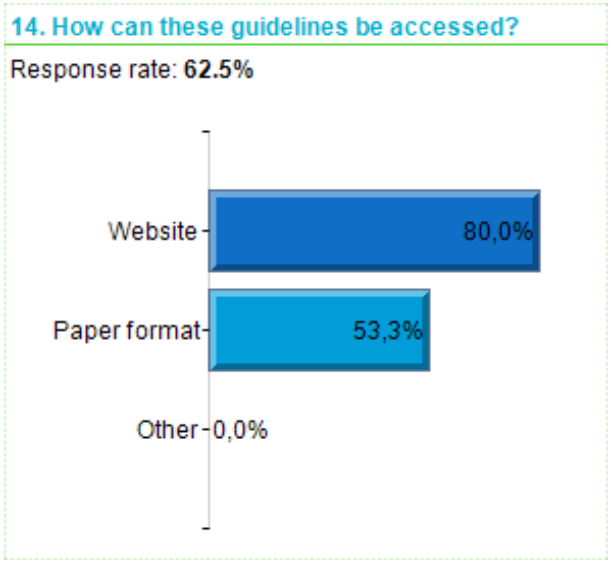
language are predominantly sought and used" making UK and USA as the main providers of such guidelines.

At the time of the questionnaire conduct, Slovakia did not have such an organization providing clinical practice guidelines in the field of oncology yet. However, it was specified by our iPAAC Slovakian partners at the Governmental Board on 9 October 2019 that an organization in charge of cancer control in Slovakia was being implemented and will be notably in charge of this activity.

They were then asked to provide the names of these organizations. More than 25 organizations in charge of writing guidelines were identified thanks to the guidelines, in addition to the organizations previously identified with the literature review. The list, including both national cancer societies as well as national bodies, is available in the appendix 5.

Most of the guidelines are written in national language. Some countries translate publications in English like Spain and Greece where respectively the Spanish and the Hellenic societies for medical oncology translate their guidelines in English. In other countries like Belgium, France, Germany, guidelines sometimes have related publication in scientific papers in English.

Most of the guidelines were available online but in some countries, only paper format was identified



3.4.3 Place of innovative immunotherapies within clinical practice guidelines

At the time of the questionnaire analysis, only half of the countries (12/23, 52%) had already included innovative immunotherapies in the treatment strategy in at least one clinical practice guideline related to oncology.

The graph below represents in green countries which were positioning innovative immunotherapies in a least one guideline related to oncology, as of October 2018.

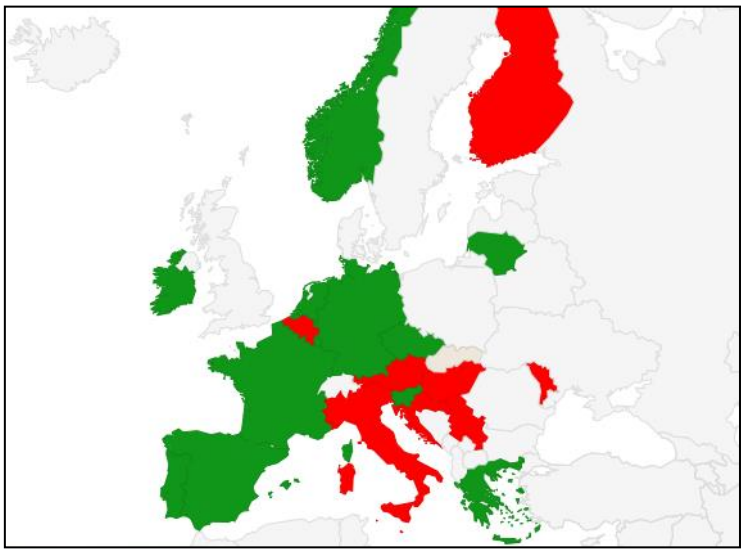


Figure 10: Countries positioning innovative immunotherapies in at least one cancer clinical practice guideline - Oct 2018

It is important to note that 7 years after the approval of the first innovative immunotherapy considered in this questionnaire (ipilimumab), and 3 years after the approval of the two anti-

PD-1 nivolumab and pembrolizumab, only half of the European countries have included these therapies in clinical practice guidelines.

3.5 Results from the questionnaire addressed to organizations in charge of providing clinical practice guidelines and WP9 partners

The questionnaire was addressed to organizations in charge of writing clinical practice guidelines. It was sent on December 5th 2018 and responses were collected up to January 3rd 2019.

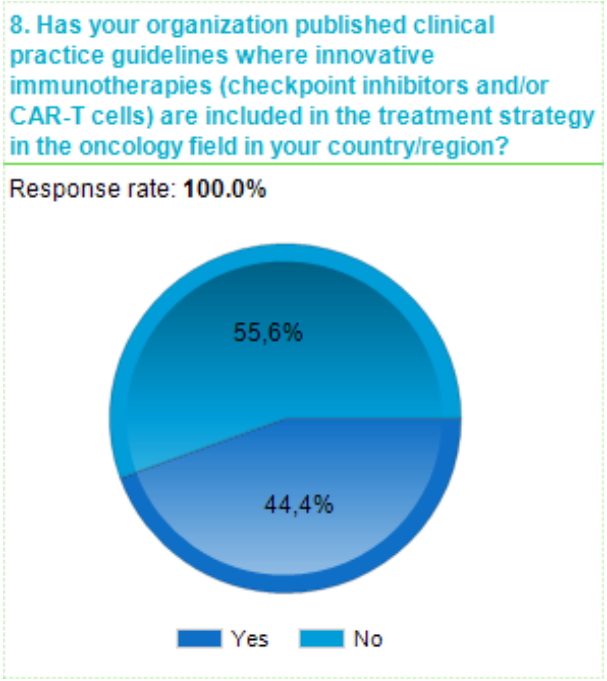
Organizations in charge of providing clinical practice guidelines were identified with results obtained from the initial literature review as well as with potential additional organizations cited in the first questionnaire.

3.5.1 Questionnaire completion

Nine answers were obtained from the following organizations:

- Cancer societies /Organ-specific societies:
  - European Society for Medical Oncology (ESMO)
  - American Society of Clinical Oncology (ASCO)
  - French Association of Urology (AFU)
- Institutional organizations:
  - French National Cancer Institute (INCa)
  - National Cancer Institute of Luxembourg (INC)
  - Catalonian Department of Health
  - General direction of health, Portugal
- Clinical centers:
  - Aviano comprehensive cancer center, Italy
  - Clinical Center Kragujevac, Kragujevac, Serbia

In addition, a reply from the Italian Association of Medical Oncology was collected in December 2019. As it was obtained a year after the first completion of the questionnaire, the feedback from AIOM is not counted with the other results and not integrated in the graphs but their feedback provided has been integrated below in the according sections below.



Among the 9 organizations who replied, 4 had published a guideline placing an innovative immunotherapy in the treatment strategy.

Tableau 14: Organizations among responders who have published a clinical practice guideline which include innovative immunotherapies in the cancer treeatment strategy and localization

Organizations	Cancer types for which a guidelines was published by this organization
ASCO	Lung cancer, pancreatic cancer
ESMO	Melanoma, lung cancer, bladder cancer, kidney cancer, head and neck cancer, colorectal cancer, breast cancer, liver cancer, hematologic cancers, toxicity of immunotherapies
INCa	Melanoma
AFU	Bladder cancer, kidney cancer, prostate, penile and testis cancer

In addition, in December 2019, the Italian Association of Medical Oncology (AIOM) had published clinical practice guidelines where innovative immunotherapies (checkpoint inhibitors and/or CAR-T cells) are included in the treatment strategy in the oncology field for the following localizations:

- Lung cancer;

- Melanoma;
- Kidney cancer;
- Head and neck carcinoma;
- Neuroendocrine tumors, in which a chapter is dedicated to Merkel cell carcinoma, and includes recommendation for use of avelumab.

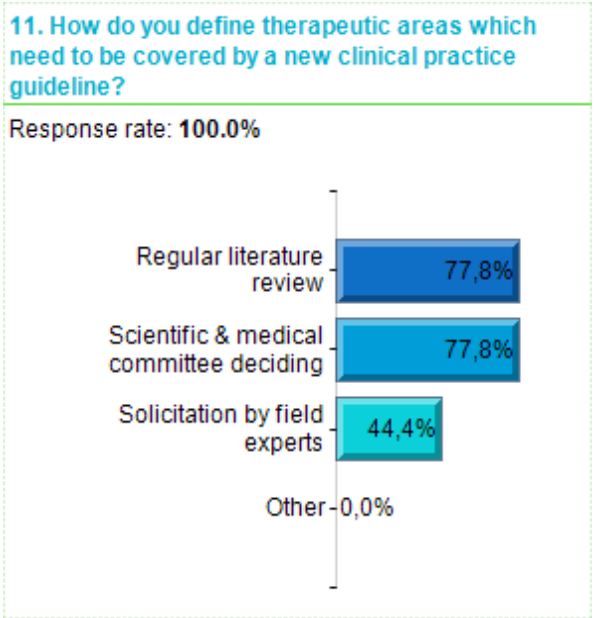
Furthermore, evidence obtained with checkpoint inhibitors is discussed in the text of the AIOM guidelines for bladder cancer and colorectal cancer, but recommendations do not include these drugs because not reimbursed by Italian National Health System as of October 2019.

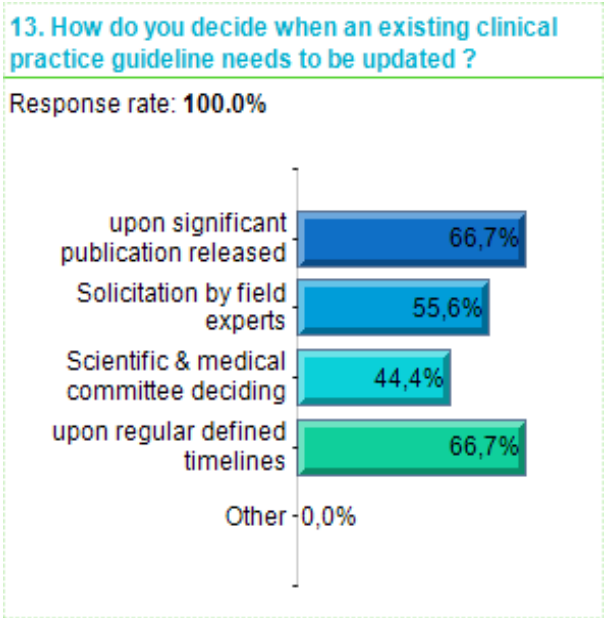
In addition, AIOM has produced a specific clinical practice guideline dedicated to management of immune-related adverse events.

3.5.2 Production and update of clinical practice guidelines

Regular literature review as well as scientific and medical committee (N = 7/9) appear to be the two most common ways to identify the need of therapeutic areas which need to be covered by a new clinical practice guidelines. Less regularly (N=4/9), solicitation of field experts is also used.

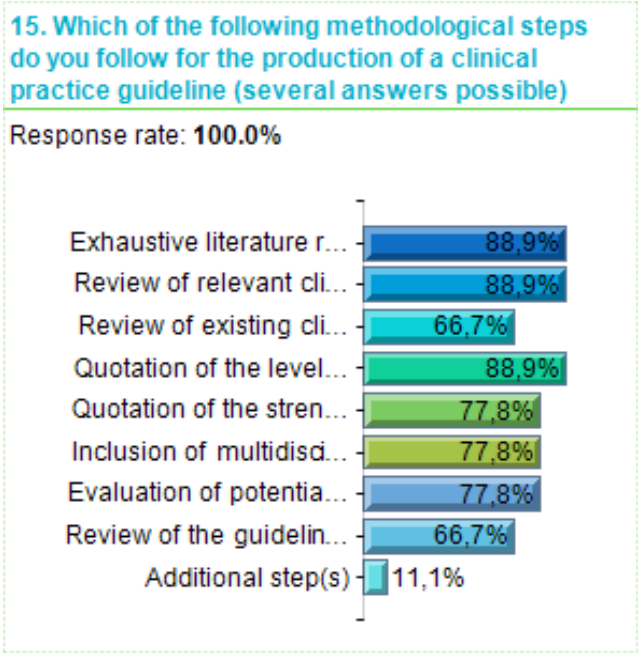
Concerning the decision to update an existing clinical practice guideline, it seems that the most commonly used triggers are significant publication released (N=7/9) and regular defined timelines (N=7/9). Less commonly, solicitation by field experts (N=5/9) and decision from scientific/medical committee (N=4/9) could be used.





Existing AIOM clinical practice guidelines already cover all major tumors. AIOM National Board can decide to commission the production of further guidelines if needed. The existing guidelines are reviewed upon regular defined timelines: every year.

Methodological steps to follow:



In the open question concerning potential additional steps, one organization pointed out that: “in order to define the work framing, we ask all the stakeholders involved in the field, to identify the clinical questions and field to treat.”

The AIOM also follow the steps below for the production of clinical practice guidelines:

- Exhaustive literature review
- Review of relevant clinical trial publications
- Quotation of the level of evidence
- Quotation of the strength of recommendation
- Inclusion of multidisciplinary experts in the group writing guidelines
- Evaluation of potential conflict of interest
- Review of the guidelines by a group of relevant experts prior publication
- GRADE methodology

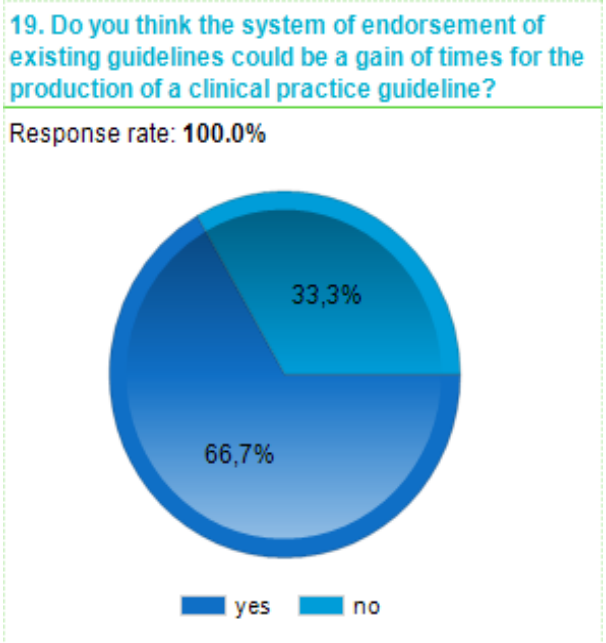
Existing endorsement systems:

ASCO has a formal process in place enabling organizations to submit for endorsement consideration. A expert panel is then constituted to draft an endorsement manuscript which is reviewed and approved by an independent committee.

INCa has implemented a labelling system.

The ADAPT method was also named by the AFU.

Opinion on endorsement systems



Comments from organizations in favor:

INCa: Yes, if the project is managed by a project manager of the agency.

ASCO: it can save a lot of time, but clear procedures are needed - for instance, do you allow any changes to the recommendations, will that offend the original developers, does it then become an adaptation, do you update the original literature search, how do you update an endorsement?

Catalonia: One of the problems of CG is the effort involved in the production that could be avoided discussing the existing CG and endorsing the most suitable

Comments from organization not in favor of endorsement system:

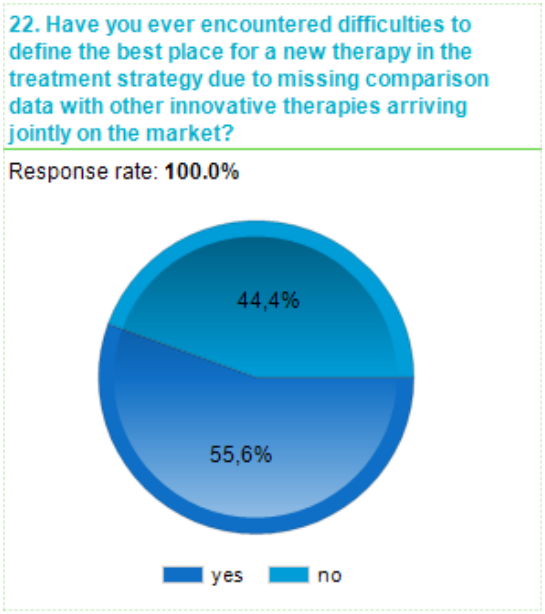
Portugal: “Priorities depend of local situation.”

AIOM guidelines are specifically produced taking into account the availability of treatments in the Italian health system. They mentioned that simple endorsement of existing guidelines produced in other contexts would not take into account this aspect.

Suggestions on ways to improve the timelines for production and update of clinical practice guidelines:

- Strong methodology and Standardized Operational Procedures appear to be a good support for the development of clinical practice guidelines
- Importance to have dedicated in-house staff with strong methodological expertise
- Reduce the scope of guidelines (or of fields to be updated) could help improving timelines
- Better training on methodological approach for medical doctors and experts involved in the production of guidelines / Honorarium
- Endorsement of existing guidelines
- Financing support
- Implement regular update with agreed timelines (e.g. every year)

3.5.3 Position of innovative therapies in cancer treatment strategies



Difficulties expressed in the following situations:

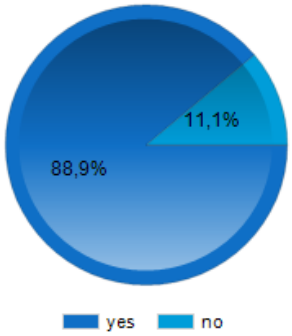
- Lack of data,
- Different points of view of the clinicians
- In the absence of comparative data, non-comparative and expert consensus can be used to help inform practice in areas of uncertainty
- Problem when drug and/or genetic testings are not available
- Approval on early phase trials, clinical trials, with small follow-up and sustained in surrogate markers.

Organizations that did not encounter any difficulties mentioned that they follow EMA approved indications.

AIOM also experienced many situations, in many tumors, with a lack of direct comparison among innovative therapies in recent years.

25. Do you think a public fund financing studies comparing innovative immunotherapies between them could be helpful to better define the place of innovative therapies in the cancer treatment strategy?

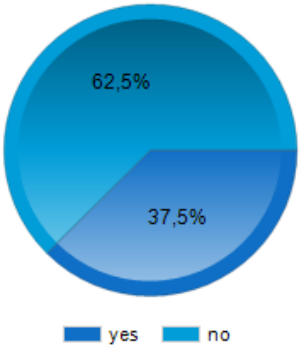
Response rate: **100.0%**



- To be noted: one country alerts on the interpretation of real world data : they think we need a careful knowledge of it before trying to modify or align with existing clinical guidelines. They also add that interventional studies are expensive and complicated to carry out once the indication is approved and reimbursed.
- Another country notes that effectiveness studies, with real-world analysis, does not substitute the need of direct comparison between innovative drugs.
- Real world data analysis could be really helpful to integrate the evidence produced by pivotal trials.

26. If yes, do you think this public fund should be financing interventional studies rather than real-world data analysis?

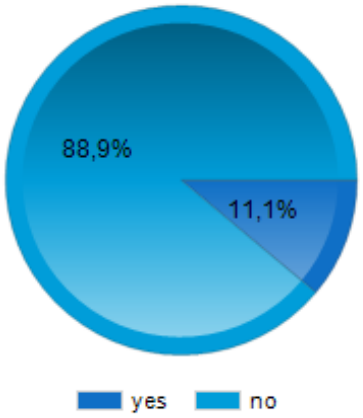
Response rate: **88.9%**



3.5.4 Off-label recommendations

27. Have you ever included in your clinical practice guidelines a recommendation for the use of an innovative therapy for an indication which did not have (or not yet) an approved marketing authorization for this specific indication in your country/region?

Response rate: **100.0%**



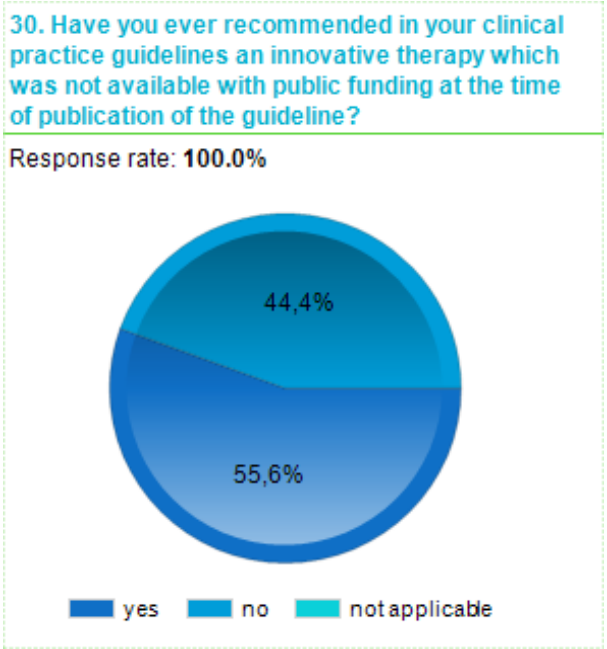
Only one organization specified that they have already included off-label recommendation for the use of an innovative therapy for an indication which did not (or not yet) have an approved marketing authorization. This organization replied that they clearly specify in their CPG that this recommendation is not approved by the reference medicine agency.

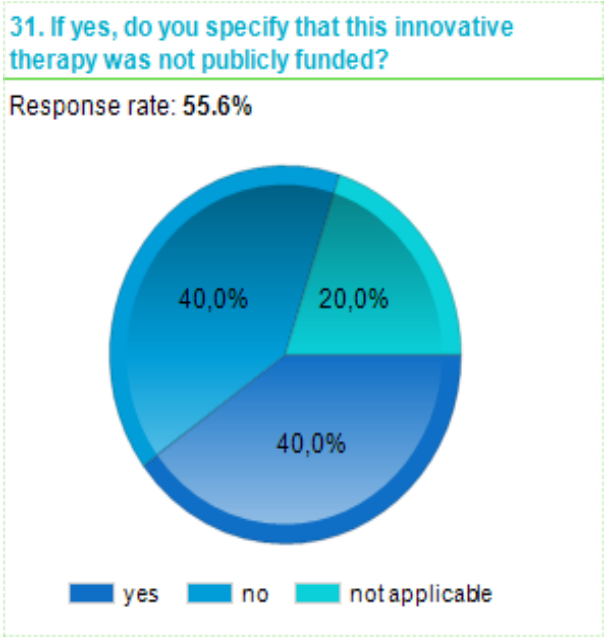
Open question regarding off-label recommendations: Do you think there are situations for which off-label recommendations could be tolerated in a clinical practice guidelines (e.g. small group of patients, specific biomarker expressed, no other therapeutic alternative …)?

Several experts agree to say that there are situations for which off-label recommendations could be tolerated in clinical practice guidelines. Indeed, it appears, for the medical community that there is a need to have guidelines including innovative therapies even though these therapies might not be approved (yet) by the competent authority. This appears very important especially for small target groups, specific biomarker expressed, pediatric population and when there is no therapeutic alternative.

However, from a governmental body/national agency point of view it is more complicate to include off-label recommendations in CPG than for medical societies. According to a public agency, one solution to allow off label recommendations is to active an early access regulation for example through the RTU (recommendation for temporary use) / ATU (authorization for temporary use) systems in France.

Regarding the AIOM, they had also already included off-label recommendations for the use of innovative therapy for an indication which did not have (or not yet an approved marketing authorization. They specified that off-label recommendations could be tolerated in selected, specific situations (evidence existing for use of a treatment, but no approval or reimbursement by Regulatory Agency). In these cases, AIOM suggests that the recommendation should always specify that the drug is not (yet) approved / reimbursed in that specific indication.





Examples of such recommendations:

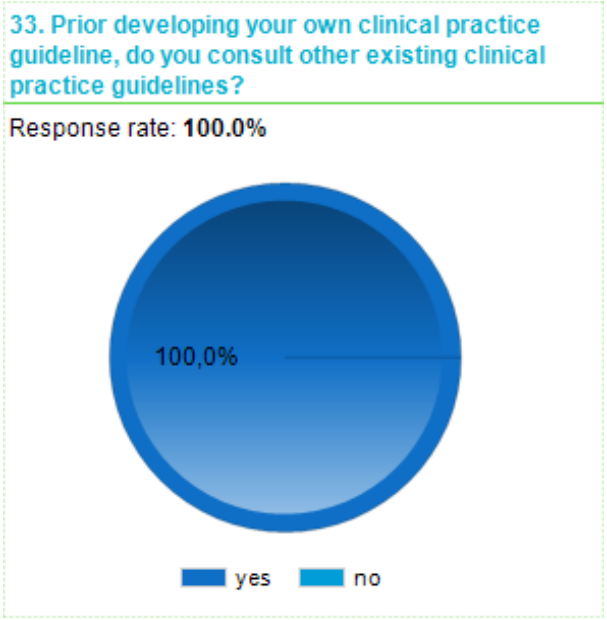
ASCO: This occurs in joint development efforts where several health settings are involved and may not be available in one or more settings - in this case, we temper the recommendation with "where available"

Portugal: Nivolumab in second line of lung cancer, after progression was registered (after treatment with first line chemotherapy) - not registered in our country.

AIOM melanoma 2019 guideline: combination of nivolumab and ipilimumab is recommended, but it is clearly specified that it is not reimbursed for use in clinical practice.

3.5.5 Visibility and accessibility of guidelines

Consultation of other existing clinical practice guidelines:



All organizations consult other existing guidelines prior developing their own.

The AIOM does not formally define the need to consult other existing clinical practice guidelines in the process of developing their own guidelines. However, it is up to the panel of each specific guideline to decide if they want to consult other guidelines.

Various answers were obtained regarding the different ways used by organizations to identify existing clinical practice guidelines:

- List of the main worldwide producers maintained up to date by internal personal
- Literature review, PubMed
- Consultation of sister societies
- Consultation of guideline repositories (GIN, former NGC)
- web based data base
- Google

Among the most cited organizations consulted prior the development of their own guidelines were notably: ESMO (6), NCCN (4), NICE (3), AUA (2), as well as AIOM guidelines, NCI/NIH, Alberta, ASCO, CAP, ASTRO, CCO, EAU, Scottish guidelines.

Communication following the release of clinical practice guidelines:

The most common ways to communicate about new or updated clinical practice guidelines seem to be the posting on the organization's website, followed by posting on national/regional platform, and publication in scientific papers.

Very heterogeneous responses were obtained for the question asking what were the most efficient ways to communicate the release of new or updated guidelines (see below for details)

In addition, ASCO mentioned that they have recently launched a guidelines App but this is too recent to assess the real impact of this potential new tool for dissemination.

What are the most efficient ways to communicate the release of new or updated guidelines?

- *INCa: congress and scientific publications*
- *ASCO: Our journal and website get a lot of traffic and we have a communication team to lead a communication strategy. We are just starting out Guidelines App, so will see how popular that is over time.*
- *ESMO: Web, members of professional societies*
- *AFU: Web*
- *Italie: Country-specific platforms, Country-specific Oncological organization platforms*
- *Catalogne: website from the Government and scientific publications*
- *Luxembourg: National release Platform, INC website (National Cancer Institute Luxembourg), Paper distribution, Email distribution*
- *Portugal: e-mail*

According to AIOM, the public release of available guidelines on their website provides a good visibility to the interested community.

7 out of the 9 organizations who answered the questionnaire thought that it could be helpful to have a platform indexing the existing clinical practice guidelines (1 not sure, and one did not reply to this question). AIOM was also in agreement to have such a platform.

4 Discussion and remaining challenges

4.1 Integration of innovative therapies in clinical practice guidelines

There is a usual and normal delay between the approval of a new therapy by regulatory agencies and its integration within clinical practice guidelines. Indeed, to ensure a high-quality document, specific methodological steps need to be followed (e.g. systematic review of the literature, collection of expert's opinion after analysis of their potential conflict of interests) which could be time-consuming.

However, as guidelines are usually used as support for decision-making for the therapeutic strategies to follow by large communities of healthcare professionals, it is important to keep a reasonable time for integration of new therapies to avoid inequalities in clinical practices.

Taking the examples of innovative immunotherapies (CAR-T cells and checkpoint inhibitors), the work conducted by the WP9 showed important variation across EU member states for the implementation of recommendations placing innovative immunotherapies within CPG. Whereas almost all European countries seem to have a system in place to produce clinical practice guidelines at the national and/or regional level, only half of these countries (12/23 as per questionnaire results) have already included innovative immunotherapies in cancer treatment strategies. Knowing that the assessment from the WP9 was performed 7 years after the first marketing authorization obtained for ipilimumab in 2011, and 3 years after approval of nivolumab and pembrolizumab, it shows quite a strong delay to implement these therapies within CPG.

The literature review conducted over the summer 2018 by the WP9 showed that there were more than 120 guidelines existing in French or English placing innovative immunotherapies in the therapeutic strategy, for all types of cancers, including 52 from European organizations and 4 from international collaborations. Most of them included adults in the scope, except one consensus agreement for elderly and one focusing on the paediatric population.

One of the specificity of checkpoint inhibitors is the very large number of localizations in which these therapies were tested and approved. This explains the various localizations identified among guidelines analysed, with a larger number for oldest approved indications such as melanoma (15 guidelines), lung cancer (15 guidelines) and kidney cancer (13 guidelines). It was however interesting to see that although the indication for bladder cancer was more recent, there were more guidelines placing checkpoint inhibitors for this therapeutic area (8 guidelines) rather than for head and neck cancer (3 guidelines) and for Hodgkin lymphoma (5 guidelines).

The complexity is that guidelines should be updated as fast as possible, but not too early. For instance; some guidelines recommended the use of immunotherapies for hepatocellular carcinoma were identified during our screening phase in August 2018. However, recent publications showed negative results in phase III trials.

Through the example of non-small cell lung cancer, we have highlighted how it could be hard to maintain up-to-date guidelines in the fast evolving field of cancer. Major changes occurred every six-month in non small cell lung lunger over the past 3 years: 3 checkpoint inhibitors were approved since October 2015, several changes of labelling were implemented, an upgrade to first line treatment was approved for a specific sub-population and more recently

the use of checkpoint inhibitors in combinations was approved. Organizations had to adapt quickly to make sure that most updated indications were taken into account.

4.2 Defining the best place of innovative therapies in cancer treatment strategies

For some indications, it was seen that the place of a similar innovative immunotherapy could differ between several updated clinical practice guidelines. This was the example for BRAF-mutated patients with unresectable or metastatic melanoma who could receive either anti-BRAF/anti-MEK or anti-PD-1 as first line treatment option. This could be explained by the fact these 2 therapies were developed in parallel. There is currently no clear evidence comparing the efficacy and safety of these 2 treatment options. With no comparative data between several new therapies arriving at the same time on the market, it is hard to define whether one treatment option should be preferred over the other one. Interestingly, this is often for these same indications that we have noticed differences in terms of reimbursement between European member states (e.g.: Portugal: no reimbursement for BRAF-mutated patients).

More than half of the experts solicited via the second questionnaire highlighted that they had already encountered some difficulties to define the best place for a new therapy in the treatment strategy due to missing comparison data with other innovative therapies arriving jointly on the market. These difficulties could be strengthened by divergence of opinions between clinicians and therapies approved in earlier stage of development (e.g. approval obtained with a phase II trial).

There are also differences in terms of access to innovative therapies at the national level which could have an impact on therapeutic strategies (e.g. decision on reimbursement, specific early access programs, …). When there is no public funding: it could be harder to define the position: about half of the experts interrogated mentioned that they have already included a recommendation of use in their CPG for a drug which was not available with public funding at the time of publication of the guideline.

One expert also rose that the lack of possibility for genetic testing at the national level could influence the position of innovative immunotherapies in cancer treatment strategies.

In this context it appears important to have more sponsored post-marketing studies to compare therapies between themselves. Unfortunately, such studies are not often sponsored by the pharmaceutical industry, this is where we could benefit from a public financing and organizational support to conduct such studies. Of course randomized controlled trials remain the gold standard to prove the efficacy of new drugs, but study conducted in real-life settings appear more and more as a solution to continue gain knowledge after marketing authorization.

The experts solicited thought for a large majority of them (90%) that a public fund financing studies comparing innovative immunotherapies between them could be helpful to better define the place of innovative therapies in cancer treatment strategies.

4.3 Acceptability of off-label recommendations in clinical practice guidelines

Clinical practice recommendations are made based on available results of clinical research studies but are not always based on approved marketing authorizations. Several recommendations for the use of innovative immunotherapies in indications which did not have yet an official marketing authorization were identified through the review of guidelines. Among the 120 guidelines analyzed, 18 were providing recommendations for an indication not approved by the referenced medicine agency, 9 were describing clinical results for an unapproved indication, 5 were referring to an off-label indication and 8 recommended inclusion into clinical trials for an unapproved indication.

The most widespread off-label recommendation was for the use of checkpoint inhibitors, particularly pembrolizumab, for MSI-H tumours, and more especially for MSI-H colorectal tumours. Indeed, 4 out of the 7 guidelines for colorectal cancer including checkpoint inhibitors in the colorectal cancer treatment strategy were from European organization whereas there was no authorized indication approved in Europe at the time of the analysis.

Additional indications are often authorized in the USA compared to Europe. This could link to some additional off-label recommendations. Indeed, there are internationally well-recognized clinical practice guidelines published in North America which based their recommendations on FDA authorizations. This could trigger the writing of off-label recommendation in European clinical practice guidelines, especially for small groups of population and when clinical trial results are poor.

From the survey conducted among experts of clinical practice guidelines, only one organization replied that they had already included off-label recommendation in their CPG. They specified in the wording of the CPG that the recommendation for this specific indication was not approved by the reference medicine agency.

Regarding the acceptability of providing recommendations for off-label indications, there was some divergence of opinion noted among experts. Several experts agree to say that there are situations for which off-label recommendations could be tolerated in clinical practice guidelines. Some examples given were: small group of patients, specific biomarker expressed, pediatric population or no other therapeutic alternative. Some experts pointed out that guidelines should be a balance of evidence and real-world clinical practice and should be based on clinical needs and scientific grounds.

However, from the perspective of governmental bodies and national agencies, it appears more difficult to include off-label recommendations than for medical societies. This difference of perspective for the 2 communities might explain the divergence of opinions noted for this question.

Moreover, it was raised that it could be important to make such off-label recommendations when clinical data supporting the evidence of a positive benefit/risk ratio is available. Indeed, in some instance, the decision not to go for marketing authorization request could be based on a business strategy rather than to unavailability of clinical data.

4.4 How could we improve the production and update of clinical practice guidelines?

The field of innovative therapies is evolving very fast, it seems to be important to have a strong methodology in place to identify fields where the impact on therapeutic strategies in very important. From our questionnaire results, regular literature reviews as well as scientific and medical committee appear to be the two most common ways to identify the need of a new clinical practice guideline in a specific area. Concerning the decision to update an existing clinical practice guideline, it seems that the most commonly used triggers are significant publication released and regular defined timelines (N=7/9).

Some ideas were highlighted to try to improve the length of production and update of guidelines such as the support from robust methodology and standardized operational procedures, dedicated in-house staff with strong methodological expertise, reduction of the scope of guidelines (or of fields to be updated), strengthen the training on methodological approach for medical doctors and experts involved in the production of guidelines, increasing financial support.

Strengthen collaboration also appear as a good way to improve the availability of clinical practice guidelines. This is especially the case for therapeutic area where there is no specific existing societies and rare types of cancers. For instance, three European organizations collaborated to write a consensus statement for the management of Merkel cell carcinoma: the European Dermatology Forum, the European Association of Dermato-Oncology, and European Organization for Research and Treatment of cancer. The French National Thesaurus of digestive oncology is also a strong network between 7 different organizations enabling frequent updates of their clinical practice guidelines and making them as a strong reference document in France in this therapeutic field.

Additionally, implementing endorsement systems could gain some time for the production of a guideline. Indeed, some organizations responded through our questionnaire that they already have systems in place to endorse CPG; and most of the organizations who replied seem to agree that such endorsement systems could gain time for production and update of CPG. However, these systems also have their limits. Experts seem to agree that clear procedures are needed, especially to anticipate the type of changes which could be allowed (without offending original developers), the potential need to update the literature review which was performed. A strong involvement both from the organization writing guidelines and from the organization endorsing the guideline are needed, with appropriate dedicated staff.

4.5 Communication on clinical practice guidelines to improve visibility

Our initial research on PubMed showed some limit in terms of visibility of European guidelines: only 10 organizations in charge of writing guidelines were identified by this way. This could be linked with the fact that very few organizations in charge of writing guidelines in Europe translate their publications in English. Indeed, as seen through the questionnaire, 90% of the national and regional guidelines are published in local language. Even though some organizations have mentioned that they try to publish related publication in scientific papers in English, only the Spanish and the Hellenic societies for medical oncology translate their all their guidelines in English. It could be interesting to promote the translation of national guidelines in English to strengthen collaboration between organizations.

In Malta for instance, where they do not have a system in place for writing guidelines, they specified that “Guidelines and protocols in the English language are predominantly sought and used” making UK and USA as the main providers of such guidelines.

It remains however quite complex to assess what is the most efficient way to communicate the release of a new or updated guideline. Indeed, responses across the different stakeholders interrogated were quite various. It went from publications on the organization’s website to communication at congresses, scientific publications and emails addressed to professional societies. Two organizations also mentioned the communication via country-specific (oncology) platforms. In addition, ASCO mentioned that they have recently launched a guidelines application but it was too recent to assess the real impact of this potential new tool for dissemination.

All of the responders admitted to consult if existing guidelines were published prior developing their own. However, when we asked about the ways to identify such guidelines, answers were quite various: consultation of a list of the main worldwide producers (maintained up to date by internal personal), literature review (PubMed, Google), and consultation of sister societies. One society mentioned the consultation of the guideline repositories “Guidelines International Network”. Nevertheless, it is mandatory to register on this website to have access to the cited publication.

Most of the experts consulted thought that it would be helpful to have a platform indexing existing guidelines. Thus, it could be interesting to implement this kind of repository platform to provide an inventory of European guidelines with free access to publication. This has been already started through the European Commission Initiative on Breast Cancer. A list of international guidelines on breast cancer care is available on the JRC website (https://healthcare-quality.jrc.ec.europa.eu/international-guidelines). The catalogue offers easy ways to filter guidelines of interest depending on the care process, developers, year of publication and other relevant keywords.