



HAL
open science

Organizational Impact of Immunotherapies in Advanced Cancers in France

Valentine Grumberg, Christos Chouaïd, Anne Françoise Gaudin, Christophe Le Tourneau, Aurélien Marabelle, Isabelle Bongiovanni-Delarozière, François-Emery Emery Cotté, Isabelle Borget

► To cite this version:

Valentine Grumberg, Christos Chouaïd, Anne Françoise Gaudin, Christophe Le Tourneau, Aurélien Marabelle, et al.. Organizational Impact of Immunotherapies in Advanced Cancers in France. *JCO global oncology*, 2023, 9, 10.1200/GO.23.00026 . hal-04190837

HAL Id: hal-04190837

<https://hal.science/hal-04190837>

Submitted on 4 Sep 2023






HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial - ShareAlike 4.0 International License

Organizational Impact of Immunotherapies in Advanced Cancers in France

Valentine Grumberg, PharmD^{1,2} ; Christos Chouaid, MD, PhD^{3,4} ; Anne-Françoise Gaudin, PharmD¹ ; Christophe Le Tourneau, MD, PhD^{5,6}; Aurélien Marabelle, MD, PhD⁷ ; Isabelle Bongiovanni-Delarozière, PhD⁸; François-Emery Cotté, PhD, PharmD¹; and Isabelle Borget, PhD, PharmD^{2,9} 

DOI <https://doi.org/10.1200/GO.23.00026>

ABSTRACT

PURPOSE In 2020, the French National Authority for Health (*Haute Autorité de Santé*) published a methodologic guide called organizational impact (OI) cartography to define and structure assessment of the OI of health technologies. As immunotherapies are associated with extended survival and improved quality of life in advanced cancer, we aimed to identify OIs that immunotherapies had on health care systems and professionals. To our knowledge, we suggest the first implementation for OI assessment on the basis of the cartography.

METHODS A literature review was conducted, and interviews with health care professionals (HCPs) were performed to identify OIs of immunotherapies. They were asked if immunotherapies had OIs classified into three macrocriteria, namely, impact on the care process (six criteria), impact on capacities and skills required (six criteria), and impact on society (four criteria). If an OI was mentioned for a criterion, information on its impact (minor/moderate/major) and its timing was collected. We considered that an OI existed when 75% of HCPs mentioned an impact for a given criterion.

RESULTS Overall, 27 HCPs were interviewed. For 12 of 16 criteria, most HCPs mentioned an impact, whereas the literature identified impacts for 11 criteria. Four criteria (skills and transfer between HCPs, scheduling capabilities, and social relationship) had consensus among HCPs and a high impact; two criteria (rhythm or care duration, working/living conditions) showed consensus but a moderate impact; two criteria (funding and scheduling capabilities cross-structure) had a high impact but no consensus. For eight criteria (as environment or inequity), there was no consensus and moderate impact.

CONCLUSION The introduction of immunotherapies for advanced cancer has had an important OI in France, regarding capacities and skills. Further research using qualitative analysis of interviews will provide more information regarding OI.

ACCOMPANYING CONTENT

 Appendix

Accepted June 29, 2023

Published August 18, 2023

JCO Global Oncol 9:e2300026

© 2023 by American Society of Clinical Oncology

Licensed under the Creative Commons Attribution 4.0 License

INTRODUCTION

With 18.1 million new cases diagnosed and 9.6 million deaths per year, cancer is one of the major public health challenges in many countries.¹ Cancer incidence will grow over time.² At this time, more than 40% of patients with cancer are eligible for immune checkpoint inhibitor (ICI) treatment.³ These treatments have rapidly become the standard of care in many indications. ICIs double the proportion of patients achieving durable response compared with the previous standard of care (25% v 11%).⁴ Between 2014 and 2020, ICIs allowed us to gain 23,788 life years and 18,369 quality-adjusted life years compared with the previous standard of care at the population treated level in France.⁵ By improving survival, ICIs have also strongly modified the management of patients with advanced cancers and have had an important budget

impact. To date, the overall organizational impact (OI) of this new therapeutic class for the health care system has not been investigated.

In France, all new treatments that have received marketing authorization are evaluated by the Haute Autorité de Santé (HAS), the National Health Technology Agency (HTA), to determine price and reimbursement status. The assessment is composed of an evaluation of the actual benefit (AB) and the clinical added value (CAV) of the health technology by Transparency Committee (TC). An economic evaluation regarding the methodology of the cost-effectiveness analysis can be performed by the Economic and Public Health Committee (CEESP). The AB rating determines the degree of reimbursement, whereas the CAV and CEESP opinions are used for price negotiation. Until recently, an OI could be

CONTEXT

Key Objective

To understand how to assess the organizational impact (OI) of health technologies on the basis of the cartography published by the Haute Autorité de Santé (HAS) and to identify OIs related to immunotherapies in advanced cancers.

Knowledge Generated

If immunotherapies have improved survival prognosis in multiple cancers, this therapeutic class has also had an OI on health care. They have increased treatment duration affecting resource utilization and had a major impact on the capabilities and skills required from health care professionals to implement the care process.

Relevance

To our knowledge, this is the first published work on OI in France using the cartography of the HAS. Health technology assessment should integrate OI analyses to understand overall consequences of innovative treatments. These analyses will help to optimize long-term health care organization.

mentioned or claimed in the dossiers submitted to the HAS for the assessment of the AB, but no methodology on how to assess the potential OI was published.⁶ For this reason, this aspect has rarely been documented.

In December 2020, the HAS published an OI cartography (OIC) for health technology assessments.⁷ In this document, the HAS sought to clarify the aspects associated with the OI of health technologies. An OI is defined as an effect, consequence, result, or repercussion created by the health technology on the characteristics and functioning of an organization or a set of organizations involved in the care or life pathway of users. To this end, the OIC helps to identify and structure the OIs according to the perspective of different actors, with a classification on the basis of three macrocriteria. To date, no information on how this institutional tool is used in health technology assessments has been published.

Based on the OIC consecutive steps published by the HAS, the objectives of this study were to use the OIC to assess in a structured manner the OI and to apply it on ICIs used for the management of advanced cancers have had on the health care system, on health care professionals (HCPs) and patients since their introduction based on literature review and interviews.

METHODS

Organizational Impact Cartography—Description

According to the HAS, an OI is evaluated through three consecutive steps: the global context of the assessment, the description of the OI using three macrocriteria and 16 subcriteria included in the cartography, and the identification of the actors concerned. The process used to assess the OI of immunotherapies is given in detail in [Figure 1](#).

The first step aims to describe the global context of the technology under assessment. This part documents if the health technology evaluated either creates a new paradigm or modifies medical care as clinically relevant alternatives already exist.

The second part of the OIC is the classification of each possible impact according to the subcriteria and macrocriteria. The cartography is constituted of the following three macrocriteria: (1) impact on the care process, (2) impact on the capabilities and skills required of HCPs and patients to implement the care process, and (3) impact on the society and the community. Within each of these macrocriteria, four to six subcriteria are defined ([Fig 1](#)—step 2).

Regarding macrocriterion 1 relative to the care process, the OIC identifies six subcriteria exploring the impact on process evolution, the quantity or type of staff involved, the material or digital resources, and the quality and safety of the environment where the process takes place.

For the evaluation of the impact on the capabilities and skills required of HCPs and patients to implement the care process (macrocriterion 2), there are six criteria related to skills and knowledge, scheduling, working and living conditions, and funding.

Finally, for macrocriterion 3 relative to the societal and community impact, the OIC evaluates whether the technology might have an impact on the community in terms of health and safety, on social inequalities or accessibility of care, on social or work relationships in terms of society as a whole, and on the environmental footprint.

The third step aims to specify which stakeholders (if any) are concerned by an IO.

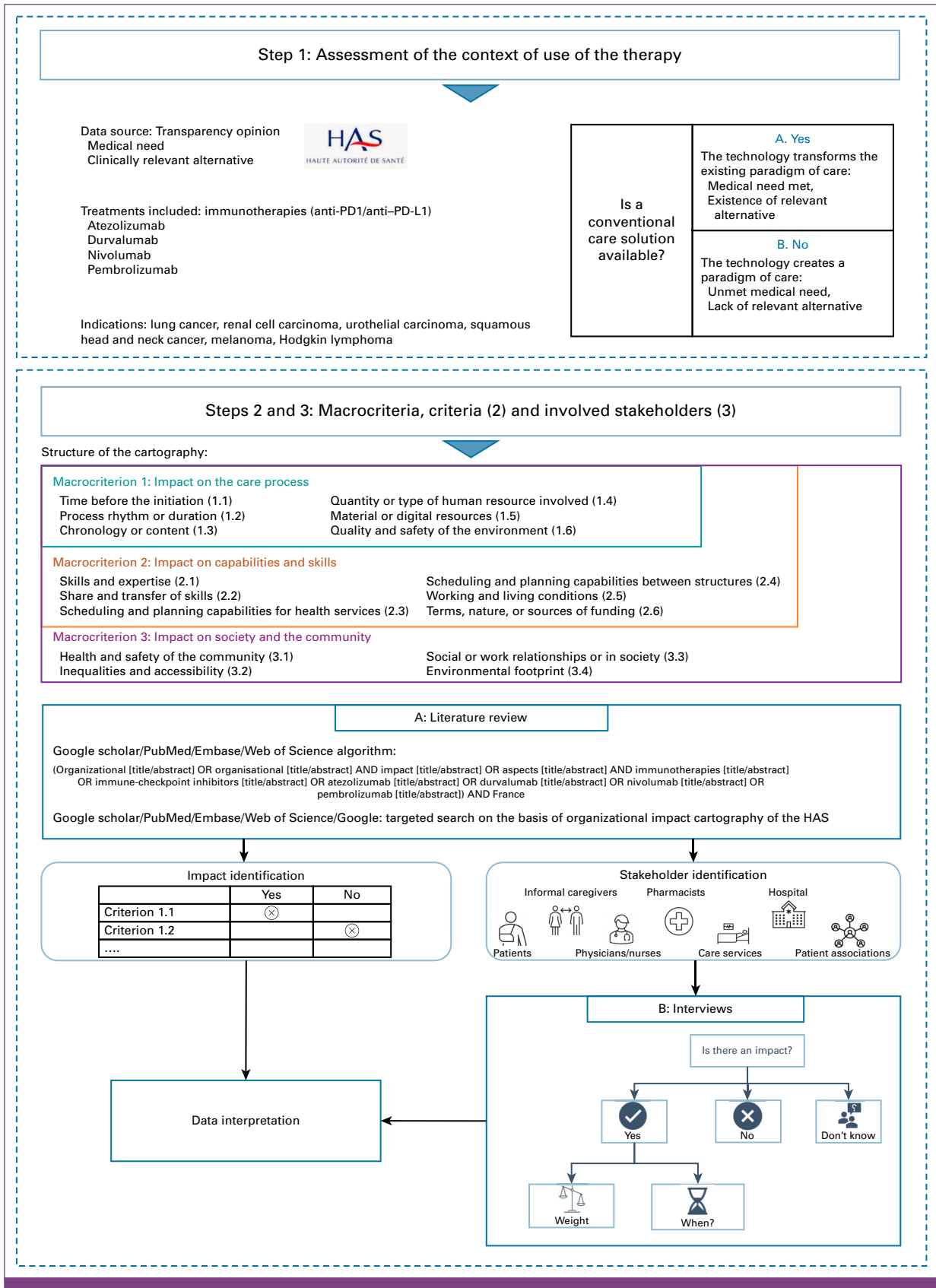


FIG 1. Organizational impact assessment process.

Step 1: Global Assessment of the Context of the Use of Immunotherapies

To document this part, a review of all TC opinions of immunotherapies, which are indicated in advanced cancers in France (atezolizumab, durvalumab, nivolumab, and pembrolizumab, in monotherapy or in combination), was performed from 2014 (first ICI availability) until July 2021 in the following indications: Hodgkin lymphoma (HL), melanoma in adjuvant and metastatic settings, non-small-cell lung cancer (NSCLC), renal cell carcinoma, small-cell lung cancer, squamous cell carcinoma of head and neck, and urothelial carcinoma. On the basis of the medical need and the presence of relevant alternatives for each indication, the context is classified into one of two categories: (1) the immunotherapy changes the paradigm of care or (2) the immunotherapy creates a paradigm of care (Fig 1—step 1).

Steps 2 and 3: Macrocriteria and Subcriteria to Assess the OI and Involved Stakeholders

Literature Review

For the scientific literature, PubMed database and conference proceedings for European Societies for Medical Oncology and French guidelines are searched. For other information, we perform searches on the Google platform and on websites of French regional and national health authorities, patients' associations, and hospitals. Newspaper articles and French government publications are reviewed.

In the targeted literature review, all publications presenting at least one organizational change listed in the OIC are retrieved. All descriptions of impact are then classified in the relevant criterion.

Interviews

Through the literature review, we identify the categories of actors potentially affected by the introduction of ICIs. Authors publishing on organizational change since the introduction of ICIs, ICI pathway or outcomes, and patients' association representatives are contacted by e-mail to propose a semistructured interview. Interviewees are asked whether someone else could be interested in the project or who should be interviewed (Fig 1—step 2). A target of at least 25–30 interviews is set to be representative of French metropolitan areas and HCPs and patients, with an opportunity to stop when information saturation is reached.

During the interviews, each person is asked if ICIs had an impact on each of the criteria included in the OIC. If they declare an impact, they must specify the period of the impact (ie, during the treatment introduction period [learning phase] or routine practice or both) and rank the impact as minor, moderate, and major. They have the opportunity to

give their perspective and, for HCPs, the perspective of their patients (Fig 1—step 2).

Data and Statistical Analyses

For the literature review, an impact on a criterion is defined when at least one publication mentioned it.

For the interviews, a quantitative analysis is first performed to estimate the percentage of HCPs and patients interviewed mentioning an impact. A consensus on impact is defined when at least 75% of the HCPs and patients mentioned an impact for any individual criterion.^{8–10} Second, the impact is weighted as follows: minor impact = 1, moderate impact = 2, and major impact = 4. An overall mean weight for each criterion is then calculated. The overall impact is also compared between categories of stakeholders (eg, physicians v nonphysicians). In the absence of a robust method to quantify a significant difference, a difference in impact count or weight between HCP categories of $\geq 30\%$ is considered relevant. The second quantitative analysis focused on the timeframe of the impact to determine whether the impact occurs during the learning phase or in routine practice. The consensus to choose the period is fixed when at least 75% mentioned an impact.^{8–10}

Using the literature and interviews, a qualitative analysis of the mentioned impact is performed.

RESULTS

Step 1: Assessment of the Context

The results of the 24 TC opinions are summarized in Table 1. For all opinions, clinically relevant alternatives already existed before the introduction of the OIC, except for durvalumab. On the basis of medical need defined as poorly or not covered, ICIs have created a new standard of care in four cases: durvalumab in NSCLC, nivolumab in adjuvant melanoma and HL, and pembrolizumab in adjuvant melanoma. For all other opinions, ICIs have transformed the existing paradigm of care.

Steps 2 and 3: Macrocriteria, Subcriteria, and Stakeholders

Literature Review

The literature review identified 58 publications or articles focusing on a potential OI according to the OIC criteria (Appendix Table A1). Impacts were observed for all three macrocriteria, concerning 11 of the 16 subcriteria. Publications explicitly mentioned no impact of the ICIs on one criterion (environmental footprint).^{15–17} No publication was identified for four criteria (1.1, 1.5, 1.6, and 3.1). HCPs publishing on OI or mentioned in publications were physicians (oncologists, specialists, immunologists, and general practitioners), pharmacists, nurses, and patient associations.

TABLE 1. Context Assessment of the Organizational Impact for Immunotherapies

Treatment	Indication	Clinically Relevant Alternatives to Immunotherapies	Medical Need Covered
Atezolizumab ¹¹	2L NSCLC	Yes	Partially
Atezolizumab + chemotherapy ¹¹	1L non-squamous NSCLC	Yes	Partially
	1L SCLC	Yes (few)	Partially
Durvalumab ¹²	Locally advanced NSCLC	No	Not
Nivolumab ¹³	Adjuvant melanoma	Yes	Poorly
	Advanced melanoma	Yes	Partially
	HL	Yes (few)	Not
	2L non-squamous NSCLC	Yes	Partially
	2L squamous NSCLC	Yes	Not specified
	2L RCC	Yes	Partially
	2L SCCHN	Yes	Partially
Nivolumab + ipilimumab ¹³	Advanced melanoma	Yes	Partially
	1L RCC	Yes	Partially
Pembrolizumab ¹⁴	Adjuvant melanoma	Yes	Poorly
	Advanced melanoma	Yes	Partially
	HL	Yes	Partially
	2L NSCLC	Yes	Partially
	1L NSCLC	Yes	Partially
	1L SCCHN	Yes	Partially
	2L urothelial	Yes	Partially
Pembrolizumab + chemotherapy ¹⁴	1L non-squamous NSCLC	Yes	Partially
	1L squamous NSCLC	Yes	Partially
	1L SCCHN	Yes	Partially
Pembrolizumab + axitinib ¹³	1L RCC	Yes	Partially

NOTE. Avelumab and cemiplimab were not included in the analysis as they were not reimbursed before 2022.

Abbreviations: HL, Hodgkin lymphoma; NSCLC, non-small-cell lung cancer; RCC, renal cell carcinoma; SCCHN, squamous cell carcinoma of head and neck; SCLC, small-cell lung cancer.

Interviews

Overall, 27 interviews were conducted. HCPs and patients' association representative were from most French regions and mostly women (56%). Most stakeholders were physicians (56%), specializing in oncology (n = 6), lung medicine (n = 2), urology or nephrology (n = 1), dermatology (n = 2), and immunology (n = 3), and one general practitioner. Other stakeholders were pharmacists (n = 6), nurses (n = 3), or patient association representatives (n = 3). HCPs included in the study worked in hospital, home care facilities, regional health care institutions, or academic societies.

There was a consensus on impact between the interviewees for a quarter of the criteria (n = 6 of 16). A quarter of the criteria have had a high impact according to weighting (n = 6 of 16).

Four criteria (health care stakeholders' skills [2.1], transferred skills between health care stakeholders [2.2], scheduling capabilities [2.3], and social relationship [3.3]) achieved high consensus and were rated as having a high impact; two criteria (rhythm or care duration [1.2], working/living conditions [2.5]) achieved high consensus with a moderate impact. Two

criteria (funding and scheduling capabilities cross-structure) were considered to have a high impact, but no consensus was achieved. For eight criteria, there was no consensus and impact was rated as moderate (Fig 2). A consensus of impact occurring in both periods was observed for half the criteria (Appendix Table A2).

Stakeholders' categories perception differed for three criteria. Most physicians considered that there was an OI on the quality and safety of the environment (criterion 1.3) and on the context in which the process takes place (criterion 1.6), whereas this was not the case for nonphysician stakeholders (Fig 3). On the contrary, most nonphysician stakeholders more frequently identified an OI on the terms, nature, or source of stakeholder funding and on the environmental footprint.

Comparison Between the Literature Review and the Interviews

The interviews enabled us to identify OI for more criteria than the literature review. The main differences concerned the impact on the care process.

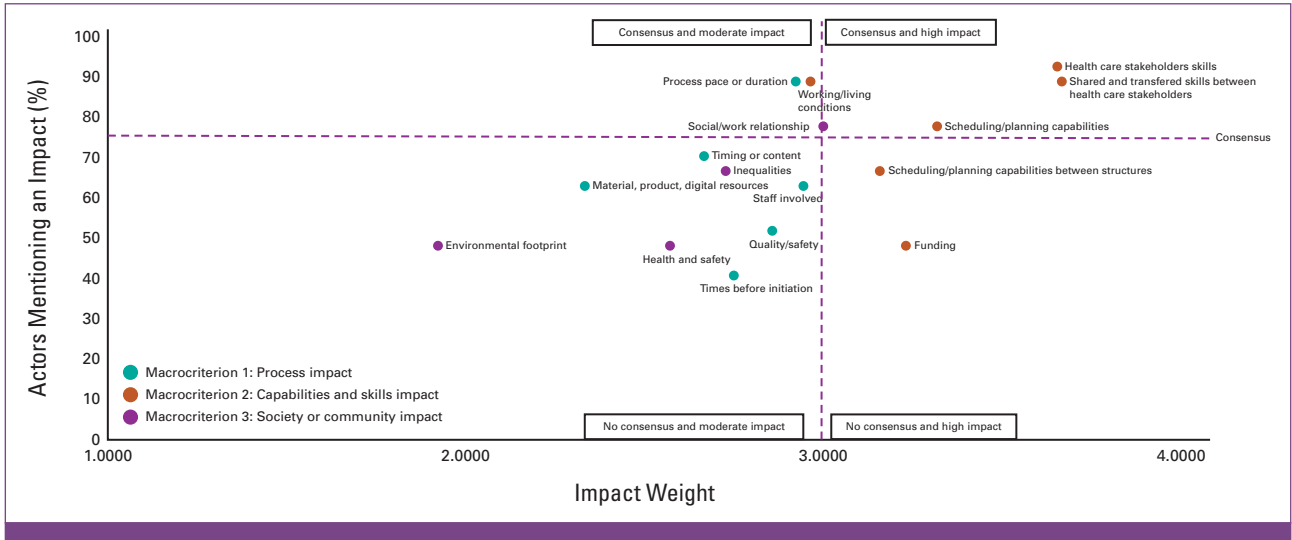


FIG 2. Percentage and weight of impacts. Seventy-five percent of actors mentioning an impact corresponds to consensus. Impact weight of ≥ 3 corresponds to high impact.

Regarding the criteria with a high impact and/or consensus (Table 2), interviews enabled us to capture more information on the OI of ICIs except for the scheduling and planning capacities for health care services (2.3). Both sources agreed

on the impact on scheduling and planning because of increased treatment duration (until disease progression or with a stopping rule; 1.2) and service saturation (1-day admission and pharmacy production; 2.3). Interviews mentioned the

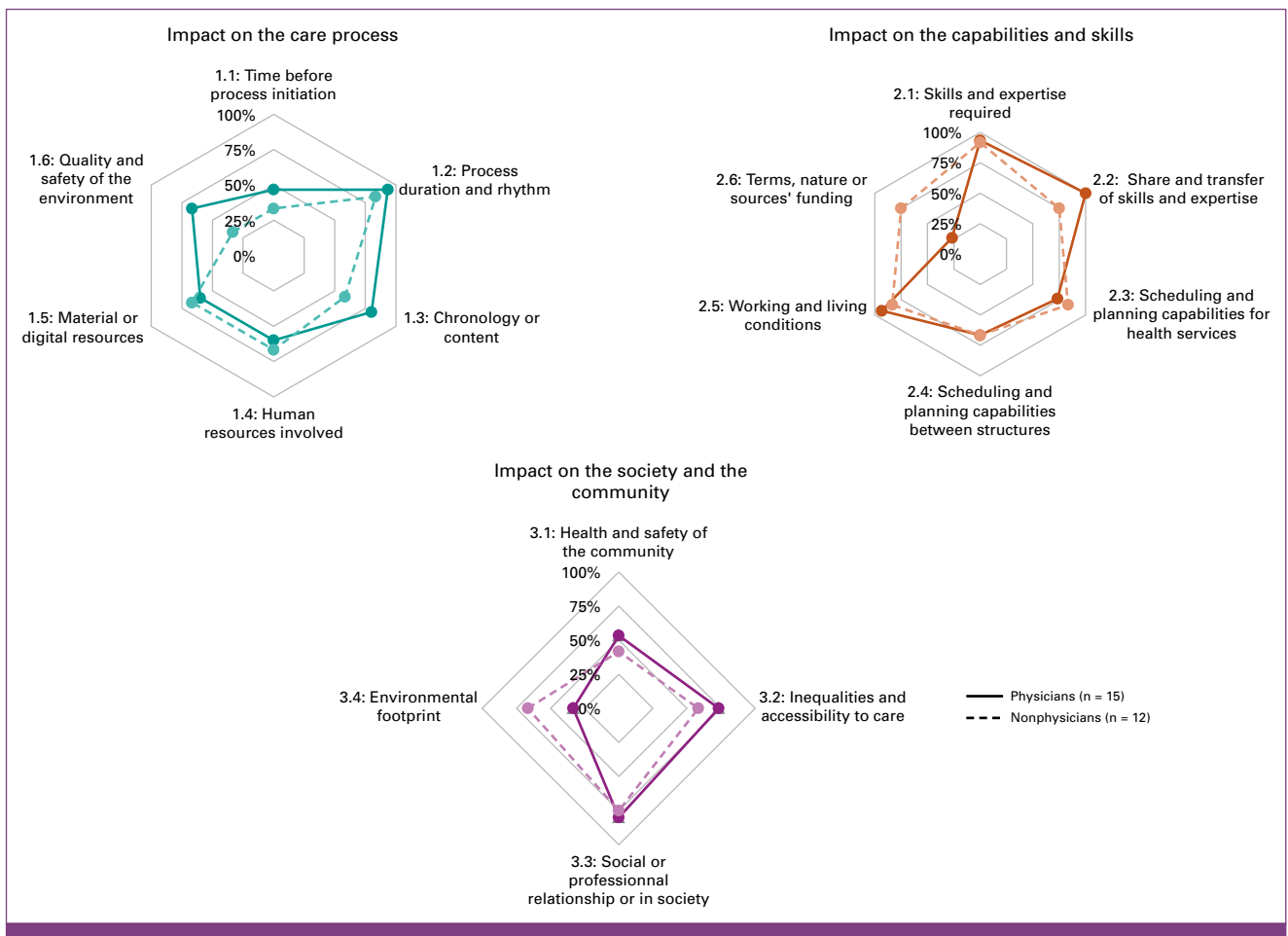


FIG 3. Percentage of impact per health care stakeholders' category.

TABLE 2. Organizational Impact Identified From the Literature and the Interviews for Criteria With Consensus or High Impact

Criteria	Information Only in the Literature	Information Only in the Interviews	Information in Both Sources
1.2: Modifies process pace or duration	Unknown stability duration of ICIs	Increased duration of pharmacovigilance case management Increased duration of production Unpredictability of treatment duration by ICIs	Treatment duration modification (increased) Frequency of administration modification (indication-dependent) Optimal duration unknown Management of AE duration
2.1: Modifies the stakeholder's required skills (knowledge, know-how, and social skills), and expertise associated with the delivery or provision of care	APN profession creation	Expensive treatment inventory management	New training for professionals New AEs management training Creation of expert networks Therapeutic education for patients
2.2: Modifies the ability to share and transfer skills, knowledge, and know-how with other stakeholders	None	Patients' experience to enrich other patients' knowledge Knowledge split with general practitioners (less involved in management of patients with cancer)	Creation of expert networks Coordination for AE management Involvement of more stakeholders Skills transfer (AE management, patient follow-up) from hospital to city or home hospitalization facilities Skills transfer between hospital professionals (oncologist, specialist, APN)
2.3: Modifies scheduling and planning capacities for health care services or the patient or informal caregiver	Only cancer centers and universities can handle with reorganization	None	Increase of treatment duration (until progression) Saturation of 1-day admission services Need to reorganize services (1-day admission) Increase of treatment production (incubator saturation)
2.4: Modifies scheduling and planning capabilities between care structures or combinations of stakeholders	None	Hospitalization at home facilities (if differentiated of 1-day admission services) Follow-up by specialists in university hospital while treatment administration in local hospital for some patients Interdepartmental or hospital networks of experts Community health care stakeholders less involved	Patient transfer between hospitals for AEs management
2.5: Modifies stakeholder's working conditions or living conditions	Quality of life: cognitive aspects Quality of life: psychological aspects Long-term quality-of-life evaluation is required	Diversification of home hospitalization facilities Toxicity management (on-call duty required) Mandatory training HCPs working conditions (hope for patients but overload)	Improved quality of life of patients/living conditions Possible return to work for patients
2.6: Modifies the terms, nature, or source of stakeholders' funding	Market access agreements	Pathway nurse funding Major cash investment for hospital Difficulty in forecasting expenses (broadening of indications) Complex management of all financing methods	Early access programs Derogatory financing sources Home hospitalization allowance
3.3: Impact in social or work relationships or in terms of society as a whole	Quality of life: cognitive aspects Quality of life: psychological aspects Long-term quality-of-life evaluation is required	Less visible toxicities Improved social and family relations Inter-HCP relationships Integration of the patient into society	Societal impact Perception of cancer/hope Return to work

Abbreviations: AE, adverse event; APN, advanced practice nurse; HCP, health care professional; ICIs, immune checkpoint inhibitors.

impact on resources in pharmacy services (2.3) caused by increased patient flow and incubator saturation. On the other hand, the literature review identified the difference in capabilities between hospital center to cope with saturation. The

adverse events caused by immunotherapies also affected the resources needed. For example, interviews mentioned the increased duration of pharmacovigilance dossier management and difficulty in predicting the treatment duration of

ICIs (1.2). Moreover, the transfer of patients between hospitals for treatment or adverse events management (2.4) was identified in both sources. In interviews, HCPs also mentioned the impact for patients since they are principally followed by specialists in university hospitals, which may differ from the hospital where their treatment is administered. The introduction of ICIs has affected the knowledge and expertise of the HCPs. Indeed, both sources mentioned the need for training of HCPs and patients caused by new types of adverse events (2.1) and the transfer of knowledge between hospital HCPs (2.2).

DISCUSSION

To our knowledge, this study provides for the first time an assessment of the OI of immunotherapies on the basis of the cartography developed by the HAS. Immunotherapies have transformed patient management in most cases.

Immunotherapies have had a strong OI, especially on the criteria related to the capabilities and skills required to implement the care process, all of which achieved consensus or were defined as high impact. Given the increased number of ICI indications, their effectiveness at prolonging survival, and the increased treatment duration until progression (or according to a stopping rule), the number of patients treated with ICI has increased over time.^{18,19} In France, between 2019 and 2020, the number of patients treated with ICI increased by more than 40%.¹⁹ The increased patients flow has had a major impact on the volume of treatments to be produced in hospital pharmacies and led to a saturation of outpatient hospitalization services. Consequently, some hospital centers have implemented a monitoring program to optimize treatment production and organization of outpatient services. In parallel, experimentations with dose and schedule optimization and home treatment administration have been implemented.²⁰⁻²²

ICIs are associated with specific immune-related side effects.²³ More than half of patients treated will experience an acute or delayed adverse event (AE), sometimes chronically (up to 40%).²⁴⁻²⁷ Given the nature of AEs associated with ICIs, oncologists and specialists have needed further training to liaise with immunologists to manage these AEs appropriately. HCPs have had to create expert networks rapidly to share knowledge affecting collaboration between care structures or services (2.4). In France, there are at least 16 multidisciplinary consultation meetings and 25 expert networks for AE management.²⁸ The outcome of these meetings should be shared widely to implement current guidelines.^{29,30}

Apart from the impact on duration (1.2) and relationships (3.3), for the criteria related to the process of care (MC1) and to societal impact (MC3), no consensus was obtained and their impact was considered mild or moderate. The significant impact on capacity and skills might be explained by the panel interviewed. Certain criteria such as

social inequalities (3.2)³¹ or the environmental footprint (3.4)³² may merit expert evaluation by specialists in these domains.

The main limitation of this study is related to knowledge of the OIC. Until the time of writing, the HAS has not published any guidelines regarding the method for criteria selection and how the results should be exploited, questioning the acceptability by the HAS of the methodology reported in this study. Moreover, the representativeness of each stakeholder category is questionable. However, physicians (almost half the sample) are the professionals most frequently dealing with immunotherapy and our findings were in general comparable between physicians and nonphysicians for 13 criteria. Therefore, for certain criteria such as funding, social inequalities, or the environmental footprint, relevant expert opinion should be considered in further analyses. Furthermore, HCPs did not have a thorough knowledge of the OIC in terms of composition and interpretation of the criteria but were interested to participate in the study that had probably biased or affected their answers. Although the HAS guidelines were designed to assess the OI of individual drugs or health technologies in each indication or setting, we explored the OI of a therapeutic class across all indications. As a result, our study did not capture any specificities that may exist within individual immunotherapies or individual indications. However, evaluating a therapeutic class as a whole also provides relevant information. For example, the expansion of indications for ICIs is the reason why the saturation of 1-day admission capacity is highlighted (criterion 2.3). We believe that evaluation of OI by therapeutic class should also be considered by the health authorities to have a comprehensive view of the impact of drug access. To our knowledge, this is the first study exploring how to conduct an OI impact assessment on the basis of the OIC prepared by the French HAS. In addition to a targeted literature review, semistructured interviews with 27 health care stakeholders enabled a broad spectrum of the different facets of patient management to be explored.

OI assessments are of growing importance for HTA, and both European Network³³ and the National Institute for Health and Care Excellence have shown interest in the question. In particular, the scale of OI assessments needs to be discussed. However, organization systems are specific for each country, and even within individual countries, there are multiple differences between hospitals. Questions remain on how the assessment of OI should be made. This study showed that a consensus on the impact of a criterion is not the only feature that should be considered important or relevant but that the magnitude of the impact also needs to be taken into account. Moreover, assessment of the OI of individual drugs in individual indications may underestimate a major OI caused by the multiplication of indications for certain drugs.

In conclusion, a literature review and interviews should be considered for OI assessment. The introduction of ICI has had a major OI in France, especially regarding capacities and

skills of health care stakeholders. For hospital outpatient services, we recommend an assessment of incoming patient flow and of the treatment duration of ICI by indication to estimate the required resources better. To prevent saturation

of outpatient services, dose or schedule optimization and home treatment should be more widely considered. Finally, to enrich knowledge on AEs, the findings of expert networks should be more widely shared.

AFFILIATIONS

¹Bristol Myers Squibb France, Rueil-Malmaison, France

²Oncostat, U1018, CESP, Inserm, Paris-Saclay University, "Ligue Contre le Cancer" Labeled Team, Villejuif, France

³Department of Chest Medicine, Créteil University Hospital, Créteil, France

⁴INSERM U955, UPEC, IMRB, Créteil, France

⁵Department of Drug Development and Innovation (D3i), Institut Curie, Paris, France

⁶INSERM U900 Research Unit, Paris-Saclay University, Saint-Cloud, France

⁷Drug Development Department (DITEP), INSERM U1015, Université Paris Saclay, Gustave Roussy, Villejuif, France

⁸Real-World Solutions, IQVIA France, Paris, France

⁹Department of Biostatistics and Epidemiology, Gustave Roussy, Paris-Saclay University, Villejuif, France

CORRESPONDING AUTHOR

Valentine Grumberg, PharmD, Bristol Myers Squibb, 3 Rue Joseph Monier, Rueil-Malmaison 92500, France; e-mail: Valentine.grumberg@bms.com.

PRIOR PRESENTATION

Presented in part at ISPOR Europe, virtual, November 30-December 3, 2021 and presented at ESMO, Paris, France, September 9-13, 2022.

SUPPORT

Supported by Bristol Myers Squibb.

AUTHOR CONTRIBUTIONS

Conception and design: Valentine Grumberg, Christos Chouaid, Anne-Françoise Gaudin, François-Emercy Cotté, Isabelle Borget

Collection and assembly of data: Valentine Grumberg, François-Emercy Cotté, Isabelle Borget

Data analysis and interpretation: All authors

Manuscript writing: All authors

Final approval of manuscript: All authors

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted.

I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/go/authors/author-center.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

Valentine Grumberg

Employment: Bristol Myers Squibb

Christos Chouaid

Honoraria: Amgen, Bristol Myers Squibb, MSD, AstraZeneca, Boehringer Ingelheim, Novartis, Pfizer, Takeda, Roche, Janssen Oncology

Consulting or Advisory Role: Roche, MSD, Bristol Myers Squibb, AstraZeneca

Research Funding: AstraZeneca (Inst), Bristol Myers Squibb (Inst), MSD (Inst), Takeda (Inst), Pfizer (Inst), Novartis (Inst), Roche (Inst), Pierre Fabre (Inst)

Travel, Accommodations, Expenses: AstraZeneca, Roche, Pfizer, MSD, Bristol Myers Squibb, Boehringer Ingelheim

Anne-Françoise Gaudin

Employment: Bristol Myers Squibb

Christophe Le Tourneau

Honoraria: Novartis, Bristol Myers Squibb, MSD, Merck Serono, Roche, Nanobiotix, GlaxoSmithKline, Celgene, Rakuten Medical

Consulting or Advisory Role: Amgen, MSD, Bristol Myers Squibb, Merck Serono, AstraZeneca, Nanobiotix, GlaxoSmithKline, Roche, AstraZeneca

Travel, Accommodations, Expenses: MSD, Bristol Myers Squibb, AstraZeneca

Aurélien Marabelle

Stock and Other Ownership Interests: Shattuck Labs, Centessa Pharmaceuticals, Dekka Biosciences, HotSpot Therapeutics, Marengo Therapeutics

Consulting or Advisory Role: Lytix Biopharma, Eisai, Pierre Fabre, AstraZeneca, Servier, Roche, Redx Pharma, Sotio, Innate Pharma, ImCheck therapeutics, MSD, OSE Immunotherapeutics, HiFiBio Therapeutics, Centessa Pharmaceuticals, Clover Biopharmaceuticals, Shattuck Labs, Dekka Biosciences, Hotspot Therapeutics, Medicxi, Depth Charge Therapeutics, BioLineRx, Gritstone Bio, Johnson & Johnson/Janssen, Third Rock Ventures, Sanofi, PegaOne, Guidepoint Global, Neogene Therapeutics, Gray Wolf Therapeutics, Adagene

Research Funding: Bristol Myers Squibb (Inst), Boehringer Ingelheim (Inst), Transgene (Inst), MSD (Inst)

Patents, Royalties, Other Intellectual Property: Monoclonal antibodies against CD81 (Stanford University)

Travel, Accommodations, Expenses: Sotio

Other Relationship: Elsevier

François-Emercy Cotté

Employment: Bristol Myers Squibb

Isabelle Borget

Honoraria: Novartis, Janssen-Cilag, Merck Serono, Roche, BMS GmbH & Co. KG, Gilead Sciences

No other potential conflicts of interest were reported.

ACKNOWLEDGMENT

We acknowledge Adam Doble from FoxyMed company for his technical assistance. We would like to thank all persons (A.K., A.L., A.M., B.E., C.D., C.F.L., C.L.T., E.G., F.B., F.S., I.T., J.B., J.P.L., K.T., L.D., L.M., M.B., M.S., M.V., N.C., N.M., N.N., O.L., P.B., P.D., S.C., V.A.) who agreed to be interviewed for their time and their contribution.

REFERENCES

1. Ferlay J, Colombet M, Soerjomataram I, et al: Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. *Int J Cancer* 144:1941-1953, 2019
2. Wilson BE, Jacob S, Yap ML, et al: Estimates of global chemotherapy demands and corresponding physician workforce requirements for 2018 and 2040: A population-based study. *Lancet Oncol* 20:769-780, 2019
3. Haslam A, Prasad V: Estimation of the percentage of US patients with cancer who are eligible for and respond to checkpoint inhibitor immunotherapy drugs. *JAMA Netw Open* 2:e192535, 2019
4. Pons-Tostivint E, Latouche A, Vaflard P, et al: Comparative analysis of durable responses on immune checkpoint inhibitors versus other systemic therapies: A pooled analysis of phase III trials. *JCO Precis Oncol* 10.1200/PO.18.00114, 2019
5. Grumberg V, Cotte FE, Gaudin AF, et al: EPH186 public health impact of immunotherapies in advanced cancers in France: A national retrospective estimate until end of 2020. *Value Health* 25: 226-227, 2022 (abstr EPH186)
6. Pascal C, Mathy C, Bongiovanni I, et al: Integrating organizational impacts into health technology assessment (HTA): An analysis of the content and use of existing evaluation frameworks. *Int J Technol Assess Health Care* 38:e80, 2022
7. Haute Autorité de Santé: Organisational impact map for health technology assessment. https://www.has-sante.fr/upload/docs/application/pdf/2021-04/organisational_impact_map_for_health_technology_assessment.pdf
8. Loblaw DA, Prestrud AA, Somerfield MR, et al: American Society of Clinical Oncology clinical practice guidelines: Formal systematic review-based consensus methodology. *J Clin Oncol* 30: 3136-3140, 2012
9. Santaguida P, Dolovich L, Oliver D, et al: Protocol for a Delphi consensus exercise to identify a core set of criteria for selecting health related outcome measures (HROM) to be used in primary health care. *BMC Fam Pract* 19:152, 2018
10. Aluwini SS, Mehra N, Lolkema MP, et al: Oligometastatic prostate cancer: Results of a Dutch multidisciplinary consensus meeting. *Eur Urol Oncol* 3:231-238, 2020
11. Haute Autorité de Santé: Atezolizumab assessment. https://www.has-sante.fr/jcms/pprd_2982779/fr/tecentriq-atezolizumab
12. Haute Autorité de Santé: Durvalumab assessment. https://www.has-sante.fr/jcms/pprd_2982846/fr/imfinzi-durvalumab
13. Haute Autorité de Santé: Nivolumab assessment. https://www.has-sante.fr/jcms/pprd_2982912/fr/opdivo-nivolumab
14. Haute Autorité de Santé: Pembrolizumab assessment. https://www.has-sante.fr/jcms/pprd_2982864/fr/keytruda-pembrolizumab
15. European Medicines Agency: Tecentriq. https://www.ema.europa.eu/en/documents/assessment-report/tecentriq-epar-public-assessment-report_en.pdf
16. European Medicines Agency: Opdivo. https://www.ema.europa.eu/en/documents/assessment-report/opdivo-epar-public-assessment-report_en.pdf
17. European Medicines Agency: Keytruda. https://www.ema.europa.eu/en/documents/assessment-report/keytruda-epar-public-assessment-report_en.pdf
18. Legoupil C, Debieuvre D, Marabelle A, et al: A microsimulation model to assess the economic impact of immunotherapy in non-small cell lung cancer. *ERJ Open Res* 6:00174-02019, 2020
19. Institut national du cancer: L'activité hospitalière en cancérologie. <https://www.e-cancer.fr/Professionnels-de-sante/Les-chiffres-du-cancer-en-France/Activite-hospitaliere>
20. Maritz C, Broutin S, Chaput N, et al: Immune checkpoint-targeted antibodies: A room for dose and schedule optimization? *J Hematol Oncol* 15:6, 2022
21. Robert C, Marabelle A, Hershner H, et al: Immunotherapy discontinuation - how, and when? Data from melanoma as a paradigm. *Nat Rev Clin Oncol* 17:707-715, 2020
22. Gobbin E, Toffart AC, Boisserie Lacroix L, et al: Immune checkpoint inhibitors and hospitalization at home in France. *Bull Cancer* 109:89-97, 2022
23. Postow MA, Sidlow R, Hellmann MD: Immune-related Adverse events associated with immune checkpoint blockade. *N Engl J Med* 378:158-168, 2018
24. Ghisoni E, Wicky A, Bouchaab H, et al: Late-onset and long-lasting immune-related adverse events from immune checkpoint-inhibitors: An overlooked aspect in immunotherapy. *Eur J Cancer* 149: 153-164, 2021
25. Horisberger K, Portenkirchner C, Rickenbacher A, et al: Long-term immune-related adverse events after discontinuation of immunotherapy. *Immunotherapy* 13:735-740, 2021
26. Johnson DB, Nebhan CA, Moslehi JJ, et al: Immune-checkpoint inhibitors: Long-term implications of toxicity. *Nat Rev Clin Oncol* 19:254-267, 2022
27. Patrinely JR Jr, Johnson R, Lawless AR, et al: Chronic immune-related adverse events following adjuvant anti-PD-1 therapy for high-risk resected melanoma. *JAMA Oncol* 7:744-748, 2021
28. Coudert V, Penel N, Le Deley MC, et al: Gestion des toxicités induites par les inhibiteurs des points de contrôle immunitaire en oncologie: Cartographie des pratiques françaises. *Bull Cancer* 109: 1217-1226, 2022
29. Schneider BJ, Naidoo J, Santomasso BD, et al: Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: ASCO guideline update. *J Clin Oncol* 39:4073-4126, 2021
30. Haanen J, Obeid M, Spain L, et al: Management of toxicities from immunotherapy: ESMO clinical practice guideline for diagnosis, treatment and follow-up. *Ann Oncol* 33:1217-1238, 2022
31. Scherpereel A, Durand-Zaleski I, Cotté FE, et al: Access to innovative drugs for metastatic lung cancer treatment in a French nationwide cohort: The TERRITOIRE study. *BMC Cancer* 18:1013, 2018
32. Seppänen AV, Or Z: The environmental sustainability of health care systems. <https://www.irdes.fr/english/reports/586-the-environmental-sustainability-of-health-care-systems.pdf>
33. Cacciatori P, Specchia ML, Solinas MG, et al: The organizational domain in HTA reports: Towards a technology-oriented assessment. *Eur J Public Health* 30:219-223, 2020
34. Cairns L, Aspeslagh S, Anichini A, et al: Cancer immunotherapy: From the lab to clinical applications—Potential impact on cancer centres' organisation. *Ecanermedicalsecience* 10:691, 2016
35. Couraud S, Westeel V, Rançon F, et al: Référentiels Auvergne Rhône-Alpes en oncologie thoracique. *Cancer bronchique non à petites cellules*. Edition, 2019. https://ressources-aura.fr/wp-content/uploads/2018/12/CBNPC_2019_VDEF.pdf
36. Danson S, Hook J, Marshall H, et al: Are we over-treating with checkpoint inhibitors? *Br J Cancer* 121:629-630, 2019
37. Denis H, Davoine C, Bermudez E, et al: Specific immunotherapies in the treatment of cancers. *Bull Cancer* 106:37-47, 2019
38. Dubois M, Ardin C, André F, et al: The revolution of immuno-oncology therapy: Review of immune checkpoint inhibitors efficacy. *Med Sci* 35:937-945, 2019
39. Escudier B, Porta C, Schmidinger M, et al: Renal cell carcinoma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 30:706-720, 2019
40. Ferreira M, Cortot AB: Quelle durée de traitement pour l'immunothérapie dans le cancer bronchique? *Rev Mal Respir* 12:339-343, 2020
41. Friedlaender A, Kim C, Addeo A: Rethinking the optimal duration of immune checkpoint inhibitors in non-small cell lung cancer throughout the COVID-19 pandemic. *Front Oncol* 10:862, 2020
42. Kourie HR, Awada G, Awada A: The second wave of immune checkpoint inhibitor tsunami: Advance, challenges and perspectives. *Immunotherapy* 9:647-657, 2017
43. CRIO: Livre Blanc: Les défis de l'immunothérapie en oncologie. <http://www.crio-immunotherapie.com/upload/Livre-Blanc-immunoth%C3%A9rapie.pdf>
44. Rabeau A, Lavesque J, Joseph C, et al: Practical issues in immunotherapy in non-small cell lung cancer: Dose, duration, rate of treatment, reintroduction. *Rev Mal Respir* 13:164-173, 2021
45. Wilkinson AN: L'immunothérapie. *Can Fam Physician* 67:174-177, 2021
46. Agence Régionale de Santé: Cahier des charges: Expérimentation de suivi domicile des patients atteints d'un cancer et traités par immunothérapie. <https://www.auvergne-rhone-alpes.ars.sante.fr/media/53191/download?inline>
47. Laparra A, Champiat S, Michot JM, et al: Prise en charge des effets indésirables de l'immunothérapie des cancers. *Rev Prat* 71:400-407, 2021
48. Pages C, Vildary C, Boulanger P, et al: Immunothérapie au plus proche du patient: l'expérience du domicile. *Ann Dermatol Venerol* 147:314-315, 2020
49. Ministère des solidarités et de la santé: Avis modificatif du comité technique de l'innovation en santé sur le projet d'expérimentation « Suivi à domicile des patients atteints d'un cancer et traités par immunothérapie. https://solidarites-sante.gouv.fr/IMG/pdf/immunotherapie_clb-avis_ctis_actualise.pdf
50. Réseau régional de cancérologie Onco-occitanie: Outils d'aide à la prescription des inhibiteurs de checkpoint en oncologie. https://www.onco-occitanie.fr/wp-content/uploads/2016/03/annonce_livreblanc_IPA_12032018.pdf
51. AFIC: Livre blanc de l'infirmière de pratique avancée en cancérologie. http://www.ecole-montsouris.fr/wp-content/uploads/2018/03/annonce_livreblanc_IPA_12032018.pdf
52. Champiat S, Lambotte O, Barreau E, et al: Management of immune checkpoint blockade dysimmune toxicities: A collaborative position paper. *Ann Oncol* 27:559-574, 2016
53. ESMO: Les effets secondaires liés à l'immuno-thérapie. Guide pour les Patients les Effets Secondaires Liés à l'Immunothérapie. <https://www.esmo.org/content/download/138227/2546564/1/FR-Guide-pour-les-Patients-les-Effets-Secondaires-Lies-a-l-Immunotherapie.pdf>
54. Galvez C: Les professionnels ont très envie de s'impliquer dans la prise en charge de l'immunothérapie à domicile. <https://www.infirmiers.com/profession-infirmiere/concepts-de-soin/les-professionnels-ont-tres-envie-de-s-impliquer-dans-la-prise-en-charge-de-l-immunotherapie-a-domicile-christelle-galvez-laureate-de-femmes-de-sante.html>
55. Hospices civils de Lyon: Immunothérapie anti-cancéreuse. <https://www.chu-lyon.fr/immunotherapie-anti-cancereuse>
56. Institut Gustave Roussy. DU Immuno-Oncologie. <https://gustaveroussy.my.site.com/formation/s/formation-academique/a0Y09000003gX7cEAE/du-immunooncologie-2023?language=fr>
57. Kotecki N: Evolution des traitements en cancérologie—Adaptation des hôpitaux de jours. Evolution des traitements en cancérologie et adaptation des HDJ. <https://studylibfr.com/doc/4748969/evolution-des-traitements-en-canc%C3%A9rologie-et-adaptation-d>
58. Kostine M, Richez C, Gottenberg JE, et al: FRI0701 French specialists and immune-related adverse events of cancer immunotherapy: A state of the art from several national expert networks. *Ann Rheum Dis* 77:869, 2018
59. Kourie HR, Klastersky J: Immune checkpoint inhibitors side effects and management. *Immunotherapy* 8:799-807, 2016
60. Lena H, Ricordel C: Adverse events of immunotherapy. *Rev Mal Respir* 9:325-331, 2017
61. Moro-Sibilot D, Audigier-Valette C, Gajj Levrà M, et al: The new clinical management in thoracic oncology in 2017. *Rev Mal Respir* 9:360-366, 2017
62. Prise en charge du cancer par l'immunothérapie. <https://demo.cepor.com/produit/prise-en-charge-du-cancer-par-immunotherapie>

63. Sicard J, Veron F: The European cancer congress from the perspective of the community pharmacist. *Actual Pharm* 58:38-43, 2019
64. Blanc JF: Impact des nouvelles combinaisons immuno-oncologiques sur la prise en charge et les parcours patients dans le traitement du carcinome hépatocellulaire. *Hépatogastro Oncologie Dig* 28:9-22, 2021
65. Cancéropole Lyon Auvergne-Rhône-Alpes. Présentation générale des missions. <https://www.canceropole-clara.com/nos-actions/animation-de-la-communaute-scientifique>
66. Créquit P, Duchemann B, Canellas A, et al: Assessment, prevention and management of toxicities of chemotherapy, anti-angiogenic and immunotherapy. *Rev Mal Respir* 10:398-407, 2018
67. Robert C: A decade of immune-checkpoint inhibitors in cancer therapy. *Nat Commun* 11:3801, 2020
68. Tree AC, Harding V, Bhangu A, et al: The need for multidisciplinary in specialist training to optimize future patient care. *Nat Rev Clin Oncol* 14:508-517, 2017
69. Centre Hospitalier Universitaire de Toulouse. Cancérologie: le succès de la nouvelle organisation. https://www.chu-toulouse.fr/IMG/pdf/chu_toulouse_trait_union_156_avec_liens.pdf
70. Centre Hospitalier Universitaire Liège: Cancer et après? https://www.chuliege.be/jcms/c2_19716756/en/institut-de-cancerologie-arsene-burny/cancer-et-apres
71. Castel H, Joly F: Immunothérapies du cancer: Quel impact sur les fonctions cognitives? [Immunotherapies of cancer: Is there any impact on patient cognitive functions?]. *Med Sci (Paris)* 36: 695-699, 2020
72. Chouaïd C, Rousseau-Bussac G, Monnet I: Quality of life of immunotherapy-treated lung cancer patients. *Rev Mal Respir* 10:487-490, 2018
73. Cotté FE, Voillot P, Bennett B, et al: Exploring the health-related quality of life of patients treated with immune checkpoint inhibitors: Social media study. *J Med Internet Res* 22:e19694, 2020
74. Domnariu PA, Noel N, Hardy-Leger I, et al: Long-term impact of immunotherapy on quality of life of surviving patients: A multi-dimensional descriptive clinical study. *Eur J Cancer* 148:211-214, 2021
75. Eseadi C, Umoke P, Nwosumma V: Immunotherapy and psychotherapy for cancer patients: A viewpoint. *Int Med J* 27:725-727, 2020
76. Kaufman HL, Atkins MB, Subedi P, et al: The promise of immuno-oncology: Implications for defining the value of cancer treatment. *J Immunother Cancer* 7:129, 2019
77. McFarland DC: New lung cancer treatments (immunotherapy and targeted therapies) and their associations with depression and other psychological side effects as compared to chemotherapy. *Gen Hosp Psychiatry* 60:148-155, 2019
78. Ceyrac T, Corny J, Raybaut C, et al: Market access agreements: Definition and features. Could MAA be defined as a solution for immunotherapy funding by French health system? *Ann Pharm Fr* 76: 265-272, 2018
79. Ministère des solidarités et de la santé: Note d'information n°DGOS/PF2/DSS/1C/2019/239. Santé, Protection sociale, Solidarité-N° 12 du 15 janvier 2021. https://sante.gouv.fr/fichiers/bo/2019/19-12/ste_20190012_0000_p000.pdf
80. Sénat: Médicaments innovants: Consolider le modèle français d'accès précoce. <http://www.senat.fr/rap/r17-569/r17-5694.html>
81. Académie Nationale de Médecine: L'immunothérapie des cancers: Penser aux personnes âgées. <https://www.academie-medecine.fr/limmunotherapie-des-cancers-penser-aux-personnes-agees/>
82. Le Figaro: Immunothérapie: En France, un accès parfois difficile à ces innovations. <https://www.lefigaro.fr/sciences/immunotherapie-en-france-un-acces-parfois-difficile-a-ces-innovations-20210222>
83. Bigay-Gamé L, Sanchis Borja M, Gernigon C, et al: Le retour au travail des patients longs répondeurs à l'immunothérapie. Correspondence en onco-thoracique, Edimark, 2021
84. Fondation ARC pour la recherche sur le cancer: Soigner un cancer par immunothérapie. https://www.fondation-arc.org/sites/default/files/2021-01/fiche_immunotherapie2020_0.pdf
85. Le Figaro: Cancer, l'espoir de vaincre la maladie. <https://www.lefigaro.fr/sciences/dossier/cancer-guerir-maladie-immunotherapie-chimiotherapie-cellules-cancereuses-sante>
86. Park R, Shaw JW, Korn A, et al: The value of immunotherapy for survivors of stage IV non-small cell lung cancer: Patient perspectives on quality of life. *J Cancer Surviv* 14:363-376, 2020
87. European Medicines Agency: Opdivo. Opdivo, INN-nivolumab (europa.eu)

APPENDIX 1. ORGANIZATIONAL IMPACT OF IMMUNOTHERAPIES IN ADVANCED CANCERS IN FRANCE

TABLE A1. Sources From the Literature Review

Macrocriteria	Criteria	Sources
1	1.1	
	1.2	Cairns et al ³⁴ Couraud et al ³⁵ Danson et al ³⁶ Denis et al ³⁷ Dubois et al ³⁸ Escudier et al ³⁹ Ferreira et al ⁴⁰ Friedlaender et al ⁴¹ Kourie et al ⁴² Livre Blanc ⁴³ Rabeau et al ⁴⁴ Robert et al ²¹ Wilkinson et al ⁴⁵
	1.3	Cahier des charges ⁴⁶ Laparra et al ⁴⁷ Pages et al ⁴⁸
	1.4	Cahier des charges ⁴⁶ Ministère des solidarités et de la santé ⁴⁹ Pages et al ⁴⁸ Réseau régional de cancérologie Onco-occitanie ⁵⁰
	1.5	
	1.6	
2	2.1	Afic ⁵¹ Champiat et al ⁵² Denis et al ³⁷ ESMO ⁵³ Galvez et al ⁵⁴ Hospices civils de Lyon ⁵⁵ Institut Gustave Roussy ⁵⁶ Kotecki ⁵⁷ Kostine et al ⁵⁸ Kourie and Klastersky ⁵⁹ Lena and Ricordel ⁶⁰ Livre Blanc ⁴³ Moro-Sibilot et al ⁶¹ Prise en charge du cancer par l'immunothérapie ⁶² Réseau régional de cancérologie Onco-occitanie ⁵⁰ Robert ⁶³
	2.2	Blanc ⁶⁴ Cancéropole Lyon Auvergne Rhône-Alpes ⁶⁵ Champiat et al ⁵² Coudert et al ²⁸ Créquit et al ⁶⁶ Denis et al ³⁷ Galvez ⁵⁴ Kourie and Klastersky ⁵⁹ Livre Blanc ⁴³ Robert ⁶⁷ Sicard and Veron ⁶³ Tree et al ⁶⁸
	2.3	Cairns et al ³⁴ Center Hospitalier Universitaire de Toulouse ⁶⁹ Denis et al ³⁷
(continued in next column)		

TABLE A1. Sources From the Literature Review (continued)

Macrocriteria	Criteria	Sources
		Kotecki ⁵⁷ Kourie et al ⁴² Livre Blanc ⁴³
	2.4	Coudert et al ²⁸ Denis et al ³⁷ Kourie et al ⁴² Livre Blanc ⁴³
	2.5	CHU Liège ⁷⁰ Castel and Joly ⁷¹ Chouaïd et al ⁷² Cotté et al ⁷³ Domnariu et al ⁷⁴ Eseadi et al ⁷⁵ Kaufman et al ⁷⁶ McFarland ⁷⁷
	2.6	Ceyrac et al ⁷⁸ Ministère des solidarités et de la santé ⁷⁹ Sénat ⁸⁰
3	3.1	
	3.2	Académie Nationale de Médecine ⁸¹ Denis et al ³⁷ Le Figaro ⁸² Livre Blanc ⁴³
	3.3	Bigay-Gamé et al ⁸³ Castel and Joly ⁷¹ CHU Liège ⁷⁰ Cotté et al ⁷³ Domnariu et al ⁷⁴ Eseadi et al ⁷⁵ Fondation ARC pour la recherche sur le cancer ⁸⁴ Le Figaro ⁸⁵ Park et al ⁸⁶
	3.4	European Medicines Agency ^{5,17,87}

TABLE A2. Period of the Impact

Macrocriteria	Criteria	Mentioned Impact, n	Impact Period, %		
			Learning Phase	Routine Phase	Both Phases
1 Impact on the care process	1.1 Modifies times before initiation of the process	11	9	36	55
	1.2 Modifies process pace or duration	24	8	25	67
	1.3 Modifies timing or content	19	11	11	79
	1.4 Modifies the number or type of staff involved in the process: quantitative view of human resources	17	0	29	71
	1.5 Modifies the type or frequency of use of products, devices, materials, equipment, infrastructure, and information systems used in the process: view in terms of material of digital resources	17	13	13	75
	1.6 Modifies the quality and safety of the environment or context in which the process takes place	14	7	29	64
2 Impact on the capabilities and skills required of stakeholders to implement the care process	2.1 Modifies the stakeholder's required skills (knowledge, know-how, and social skills) and expertise associated with the delivery or provision of care	25	24	0	76
	2.2 Modifies the ability to share and transfer skills, knowledge, and know-how with other stakeholders	24	8	4	88
	2.3 Modifies scheduling and planning capacities for health care services or the patient or informal caregiver	21	0	24	76
	2.4 Modifies scheduling and planning capabilities between care structures or combinations of stakeholders	18	17	17	67
	2.5 Modifies stakeholder's working conditions or living conditions	24	4	17	79
	2.6 Modifies the terms, nature, or source of stakeholders' funding	13	0	38	62
3 Impact on the society and the community	3.1 Impact on community in terms of health and safety	13	8	15	77
	3.2 Impact on social inequalities or accessibility of care	18	28	0	72
	3.3 Impact in social or work relationships or in terms of society as a whole	21	0	5	95
	3.4 Impact on environmental footprint	13	15	15	69