MAY 2018

CURRENT STATUS AND KNOWLEDGE

SPECIFIC IMMUNO-THERAPIES IN CANCER TREATMENT

/ Summary

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INSTITUT NATIONAL DU CANCER

FRENCH NATIONAL CANCER INSTITUTE

Created by the Public Health Policy (France) Act of 9 August 2004, the French National Cancer Institute is the health and scientific agency responsible for coordinating actions against cancer in France.
Set up as a public interest grouping, it brings together the State, major associations involved in combating cancer, health insurance funds, hospital federations, and research bodies.
Its roles

- Ensure a comprehensive approach to cancerous diseases
- Promote innovation
- Issue expert reports and guidelines for decision-makers and health care professionals
- Steer regional oncology organisations
- Analyse data with a view to optimal guidance of action
- Provide information and broadcast cancer-related knowledge

INTRODUCTION

Immunotherapy essentially acts upon the patient's immune system to give it the ability to attack cancer cells.

In this field, the range of anticancer drugs available has seen major changes with the introduction onto the market of new specific immunotherapy drugs, checkpoint inhibitors (anti-PD-1, anti-PD-L1, anti-CTLA-4), the mechanism of action of which is illustrated below (1). 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.

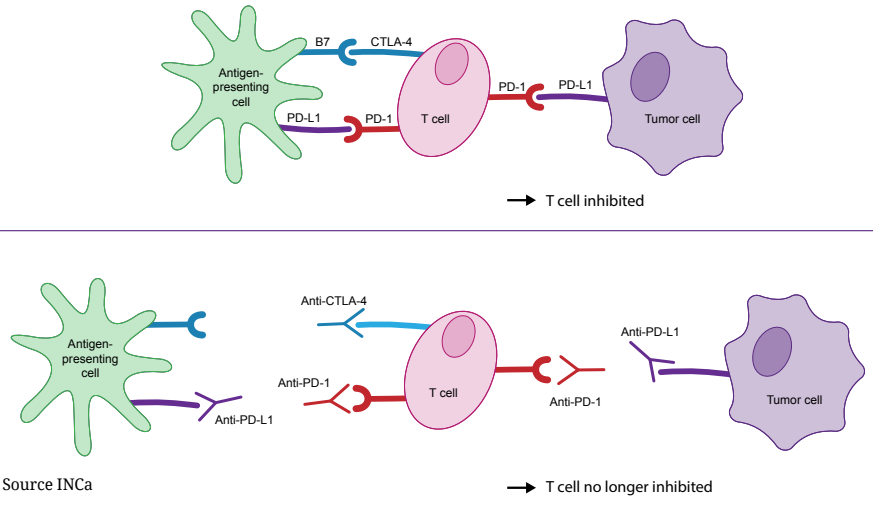
In the near future in France, other specific immunotherapy drugs, this time based on cellular and gene therapy, which are advanced therapy medicinal products (ATMPs), CAR-T cells (Chimeric Antigen Receptor-T, CAR-T cells), will be added to this array of treatments.

In this type of treatment, 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. This cell production helps prevent rejection scenarios by overcoming the context of prior HLA recognition. Specific receptors expressed on the surface of the modified T cells, known as CAR-T cells, will enable them to detect antigens present on the surface of the tumour cells and provide co-stimulatory proteins of the immune response (1).

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. In addition, further ethical and social challenges are involved, which are difficult to grasp in the literature due to the small number of existing publications referring to this topic.

As such, the French National Cancer Institute decided to devote its annual thematic report to specific immunotherapies by targeting checkpoint inhibitors and CAR-T cells more specifically. This report is particularly intended to present the current status of clinical development, the arrival onto the market and safety profile of these therapies, as well as provide an analysis of the various associated challenges. It is primarily aimed at health care professionals, French institutions and health authorities, along with other stakeholders. This summary contains the key points of this report.

FIGURE 1: Mechanism of action of anti-PD-1, anti-PD-L1 and anti-CTLA-4 therapies



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A WEALTH OF CLINICAL DEVELOPMENT

The clinical development of checkpoint inhibitors and CAR-T cells is intense. A query on clinicaltrial.gov (2) submitted in July 2017 identified more than 1500 ongoing clinical trials, studying:

- 15 anti-PD-1 therapies in 733 clinical trials, 83 in phase III;
- 8 anti-PD-L1 therapies in 311 clinical trials, 50 in phase III;
- 3 anti-CTLA-4 therapies in 282 clinical trials, 39 in phase III;
- 34 different targets targeted by CAR-T cells in 189 clinical trials (of which 86 targeting CD19).

This represents more than 285,000 patients included or to be included.

CHECKPOINT INHIBITORS

Around twenty sites are concerned by the development of checkpoint inhibitors. For anti-PD1 therapies, the two cancers most concerned in phase III are lung cancer and melanoma, corresponding to the two sites in which nivolumab (Opdivo®) and pembrolizumab (Keytruda®) were granted their first marketing authorisation (MA). Anti-PD-1 therapies have been proven to be effective or are under evaluation in many sites, but for some cancers, developments have slowed down or even been abandoned due to insufficient activity or unacceptable toxicity. As such, for example, current phase III developments in breast and colorectal cancers are restricted to subgroups of patients in whom anti-PD1 therapies appear to be active (triple negative breast cancer and high microsatellite instability colorectal cancer). Some studies evaluating pembrolizumab in multiple myeloma in association with dexamethasone and with immunomodulatory drugs (IMIDs) have moreover been discontinued due to an increased risk of death (3).

Furthermore, a substantial proportion of clinical trials relate to associations including one or more immunotherapies. Over half of the phase III clinical trials evaluate checkpoint inhibitors in association with at least one other therapy (anti-PD-1: n=42/83; anti-PD-L1: n=33/50; anti-CTLA-4: n=30/39). These generally consist of associations with conventional chemotherapies or with another specific immunotherapy.

CAR-T CELLS

In 2017, 94% of the ongoing clinical trials with CAR-T cells were phase I and I-II trials. The CAR-T cells studied have varied targets, conveying the diversity of the range of treatments under development.

The first autologous CAR-T cells, i.e. produced from the patient's own T cells, have been proven to be effective in haematological cancers; however, numerous studies are ongoing to evaluate their potential efficacy in the treatment of solid tumours.

New generations of CAR-T cells are under development: they exhibit structural enhancement intended to amplify their effect.

Allogenic CAR-T cells, produced from a donor's T cells, are also under development and some of these may help standardise the production and use of these therapies ("universal CAR-T cells").

PROGRAMMES SUPPORTED BY THE FRENCH NATIONAL CANCER INSTITUTE

INCa-designated early phase trial centres (CLIP²), investigation centres specialised in early phase trials of new drugs, receive logistic and financial support from the French National Cancer Institute. The annual CLIP² activity survey highlighted the significant increase in the number of new clinical trials relating to specific immunotherapies:

- 80 new clinical trials of this type were opened in these centres in 2016;
- the number of trials studying checkpoint inhibitors increased from 27 in 2015 to 55 in 2016;
- most of these related to anti-PD-1 and anti-PD-L1 therapies, with 30 and 23 new trials, respectively;
- 1601 patients were included in 2016 in clinical trials studying specific immunotherapies in CLIP² centres.

The aim of the AcSé clinical research programme is to offer and secure access outside the scope of an MA to therapies already approved in another indication. The treatments are then studied in phase II clinical trials open to adult and paediatric cancer patients, having experienced treatment failure and unable to benefit from an active clinical trial. Launched in 2013, the Acsé programme is continuing to evolve and offers new regimens based on emerging therapeutic innovations. As such, the arrival of anti-PD-1 therapies onto the market resulted in two new AcSé trials being set up in the first half of 2017. Their objective is to study nivolumab and pembrolizumab in some rare cancers with support from the INCa-designated rare cancer network organisation. As at 1st January 2018, 51 patients have been included in the AcSé nivolumab trial and 49 in the AcSé pembrolizumab trial.

CHECKPOINT INHIBITORS AUTHORISED IN THE EUROPEAN UNION AND CAR-T CELLS AUTHORISED IN THE UNITED STATES

TABLE 1: OVERVIEW OF THE TYPES OF CANCERS FOR WHICH CHECKPOINT INHIBITORS HAVE (AT LEAST) ONE APPROVED THERAPEUTIC INDICATION IN THE EUROPEAN UNION

	CHECKPOINT INHIBITORS				
	anti-CTLA-4	anti-PD-1		anti-PD-L1	
Cancer types*	Ipilimumab (Yervoy®)	Nivolumab (Opdivo®)	Pembrolizumab (Keytruda®)	Avelumab (Bavencio®)	Atezolizumab (Tecentriq®)
Melanoma	2011	June-15	July-15		
Non-small cell lung cancer		Oct-15	Aug-16		Sept-17
Renal cell carcinoma		Apr-16			
Classical Hodgkin's lymphoma		Nov-16	May-17		
Squamous head and neck cancer		Apr-17			
Urothelial carcinoma		June-17	Aug-17		Sept-17
Merkel cell carcinoma				Sept-17	

* The precise wording of the indications is given in the report.

CHECKPOINT INHIBITORS

As at 1st February 2018, five checkpoint inhibitors are authorised in the European Union in seven different types of cancers. The sites covered by the MAs of these various drugs are given in the table below, coupled with the date of granting of the invention. These MAs are supported by pivotal clinical trials demonstrating in the case of over half the extension of overall survival with a checkpoint inhibitor treatment, compared to a reference treatment (4–8).

CAR-T CELLS

The registration of two CAR-T cell drugs in the United States is based on non-comparative, open-label phase II trials. The sites concerned by the U.S. indications and the dates on which approval was granted are summarised in the table below (9, 10). In the light of the very promising response rate, the arrival of CAR-T therapies onto the European market is eagerly awaited and should be anticipated due to their specific features.

TABLE 2: CAR-T CELL DRUGS APPROVED IN THE UNITED STATES

Drug (product name)	Sites concerned by U.S. indications*	FDA approval date
Tisagenlecleucel (Kymriah™)	B-cell acute lymphoblastic leukaemia	30 August 2017
Axicabtagene ciloleucel (Yescarta™)	Lymphoma	18 October 2017

* The precise wording of the indications is given in the report.

MOVING TOWARDS MORE PERSONALISED MEDICINE

Checkpoint inhibitors fall within the category of "precision medicine". This term refers to medicine based on treatments developed using more enhanced knowledge of the biological mechanisms leading to the appearance and growth of tumours. The expression of certain biomarkers helps identify patients who respond better to a treatment than others. As such, some MAs require prior testing for predictive biomarkers:

- PD-L1 expression: the European MA restricts the prescription of pembrolizumab in the first-line treatment of non-small cell lung cancer to patients with over 50% tumour cells expressing PD-L1, as PD-L1 expression is associated with a superior treatment response (7);
- microsatellite instability: "agnostic" approval has been granted for pembrolizumab by the FDA for cancer treatment, for all histological types, in patients carrying a DNA repair gene abnormality (dMMR), or exhibiting high microsatellite instability (MSI-H) (11).

Nevertheless, sample quality heterogeneity and the variation of gene expression over time represent limiting factors, inherent to detection approaches using tumour samples. Furthermore, the feasibility and roll-out of these tests on a national scale impact the choice of immunotherapy in routine practice, and therefore potentially therapeutic strategies.

To date, a number of potential biomarkers have been identified, but their relevance in clinical practices and their level of validation are very variable. The identification and validation of predictive biomarkers remain major challenges in clinical research in this field so as to differentiate between responder patients and non-responders more clearly and define the target populations where the benefit/risk ratio of these drugs is positive.

DISRUPTION OF THERAPEUTIC STRATEGIES

CHECKPOINT INHIBITORS

The arrival of checkpoint inhibitors onto the market has brought about a re-evaluation of the therapeutic strategies of some cancers, particularly advanced melanoma (non-resectable or metastatic, stage IIIB/IV), metastatic non-small cell lung cancer, and advanced renal carcinoma. By adding to the array of therapies currently available, checkpoint inhibitors as such offer the possibility of new lines of treatment, also potentially deferring the need for palliative care.

The redefining of these therapeutic strategies in best practice guidelines is a major challenge in terms of optimal use. However, such redefining sometimes comes up against methodological obstacles in the absence of comparative clinical trials against the current gold-standard treatments.

The question of the duration and optimal dose of checkpoint inhibitor treatment for each cancer site also remains unresolved failing conclusive clinical data. As such, while the MA for ipilimumab recommends four treatment cycles in melanoma, the MAs for anti-PD-1 and anti-PD-L1 therapies recommend administration "until disease progression or the onset of unacceptable toxicity" or "while a clinical benefit is observed or until the patient can no longer tolerate the treatment" (4–8).

CAR-T CELLS

CAR-T cell treatment, for its part, is viewed by some experts as a revolution in the treatment of some haematological cancers. Moreover, adoptive cellular immunotherapy has been identified as the "Advance of the year 2018" by the American Society of Clinical Oncology (ASCO) in its 13th annual report on progress against cancer (12).

Nevertheless, in order to anticipate their arrival in France, in particular that of the two medicinal products previously granted approval in the United States, it is necessary to clearly define the profiles of eligible patients and the role of CAR-T cell reinjection. Comparative studies between CAR-T cells and haematopoietic stem cell grafts are awaited to refine the definition of the therapeutic strategies.

A SPECIFIC SAFETY PROFILE FOR USE

CHECKPOINT INHIBITORS

The arrival of new therapies has brought about a paradigm shift in the management of adverse reactions. Indeed, these drugs are for the most part associated with potentially severe and sometimes unpredictable immune-mediated adverse reactions (imARs). These may arise from the start of immunotherapy and up to several months after the end of the treatment. ImAR management is frequently based on prescribing immunosuppressive treatment. These imARs require different prevention, follow-up and management measures to conventional chemotherapy treatments. In this context, it is essential that hospital and non-hospital health care professionals receive the correct information on these measures. To this end, the French National Cancer Institute drafts guidelines on the prevention and management of adverse reactions due to anticancer treatments (available at e-cancer.fr) and is currently developing guidelines on checkpoint inhibitors.

Due to this immunological specificity and the very broad spectrum of adverse reactions liable to arise with these drugs, the role of organ specialists in their prevention and management, working closely with oncologists or haematologists, is crucial. While skin conditions and endocrine dysfunctions (anterior pituitary insufficiency, dysthyroidism, diabetes) have been cited extensively, other adverse reactions have been identified in real-life scenarios, such as cardiac toxicities for anti-PD-1 therapies.

This final point highlights the benefit of monitoring checkpoint inhibitors in real-life scenarios due to the relative lack of follow-up on their safety profile for use, the limited number of patients included in clinical trials, and the speed at which these treatments are being rolled out. Such monitoring involves both the pharmacovigilance system and the collection of data in real-life scenarios via specific studies. Such studies further help monitor the methods of use of drugs and off-label prescriptions.

A risk of increased fatigue has also been observed with checkpoint inhibitors. Fatigue remains the symptom experienced most frequently by patients treated for cancer and may impact patient quality of life. However, it is difficult to draw conclusions in respect of the impact of checkpoint inhibitors on quality of life. Indeed, its study remains complex due to the subjective nature of the measurement and the lack of specific studies.

CAR-T CELLS

In the summaries of product characteristics of the two FDA-approved anti-CD19 CAR-T cell products, particular focus is placed on two types of potentially life-threatening adverse reactions for the patient.

Firstly, cytokine release syndrome generally occurring during the first week following the infusion of CAR-T cells and which may last for up to seven days. This syndrome is conveyed clinically by the presence of fever, hypotension, tachycardia, hypoxia, shivering, heart arrhythmia. The prevention and management of this adverse reaction particularly require the prescription of antibodies against soluble and membrane interleukin-6 receptors, such as tocilizumab, outside the scope of an MA (product marketed in France: Roactemra®), and the involvement of the intensive care department.

Second, neurological impairment may arise in the first eight weeks after injecting CAR-T cells and may cause encephalopathy, headaches, tremors, anxiety and epilepsy in the patient. This adverse reaction may last for approximately two weeks.

It should be noted that, as genetically modified organisms are involved, long-term patient follow-up is required to supplement knowledge on the safety profile for use, particularly virological, of CAR-T cells.

The issue of real-life follow-up of these drugs is crucial and must be anticipated prior to the marketing in France, or even in the European Union, of CAR-T cells. Due to specific issues associated with the medium- and long-term safety of use of CAR-T cells and with their expected target population, which is currently restricted, the implementation of exhaustive follow-up, for example via a patient registry, should be anticipated. In this regard, a working group met on 9 February 2018 at the European Medicines Agency (EMA) to discuss this issue (13).

USE OF CHECKPOINT INHIBITORS IN FRANCE

PRESCRIPTION AND DISPENSING CONDITIONS

The checkpoint inhibitors marketed in France are list I drugs, reserved for hospital use. They are administered by intravenous infusion in a hospital setting. Prescriptions are exclusively reserved for specialists (oncologists/haematologists).

TREATMENT ORGANISATION: SESSIONS VERSUS IN-PATIENT CARE

These treatments are generally administered as a day case, under suitable supervision, and require medical time and an assigned nurse. Only 5% of administrations of nivolumab, 9% for pembrolizumab and 11% of those of ipilimumab, were conducted under in-patient care in 2016 (ATIH data, INCa processing). In view of the constantly rising patient register, hospital staff will need to adapt to the ensuing logistic constraints.

NUMBER OF PATIENTS TREATED

Since 2014, a decrease in the number of new patients treated with ipilimumab has been observed (1080 new patients in 2014, 561 new patients in 2015 and 322 new patients in 2016). Conversely, an increase in the number of new patients treated with nivolumab is observed (3966 new patients in 2015 and 8720 in 2016) and pembrolizumab (903 new patients in 2015 and 1023 in 2016) (ATIH data, INCa processing).

TARGET POPULATION

The French National Authority for Health (HAS) has estimated the target populations in France for ipilimumab, nivolumab and pembrolizumab, for all indications combined, at approximately 20,000 new patients per year (14–31).

MEDICAL BENEFIT AND IMPROVEMENT IN MEDICAL BENEFIT

As at 1st February 2018, HAS has rated the medical benefit (SMR) and the improvement in medical benefit (ASMR) of three checkpoint inhibitors (pembrolizumab, nivolumab and ipilimumab) for a total of twelve therapeutic indications relating to five cancer sites: melanoma, non-small cell lung cancer (NSCLC), renal carcinoma, Hodgkin's lymphoma and squamous head and neck carcinoma (14–31):

- over 90% of the indications examined are community-approved (84% "high" SMR and 8% "moderate" SMR);
- for almost 70% of the indications examined, specific immunotherapies provide therapeutic progress over existing treatments (particularly four "moderate" ASMR III ratings assigned, i.e. 33% of indications).

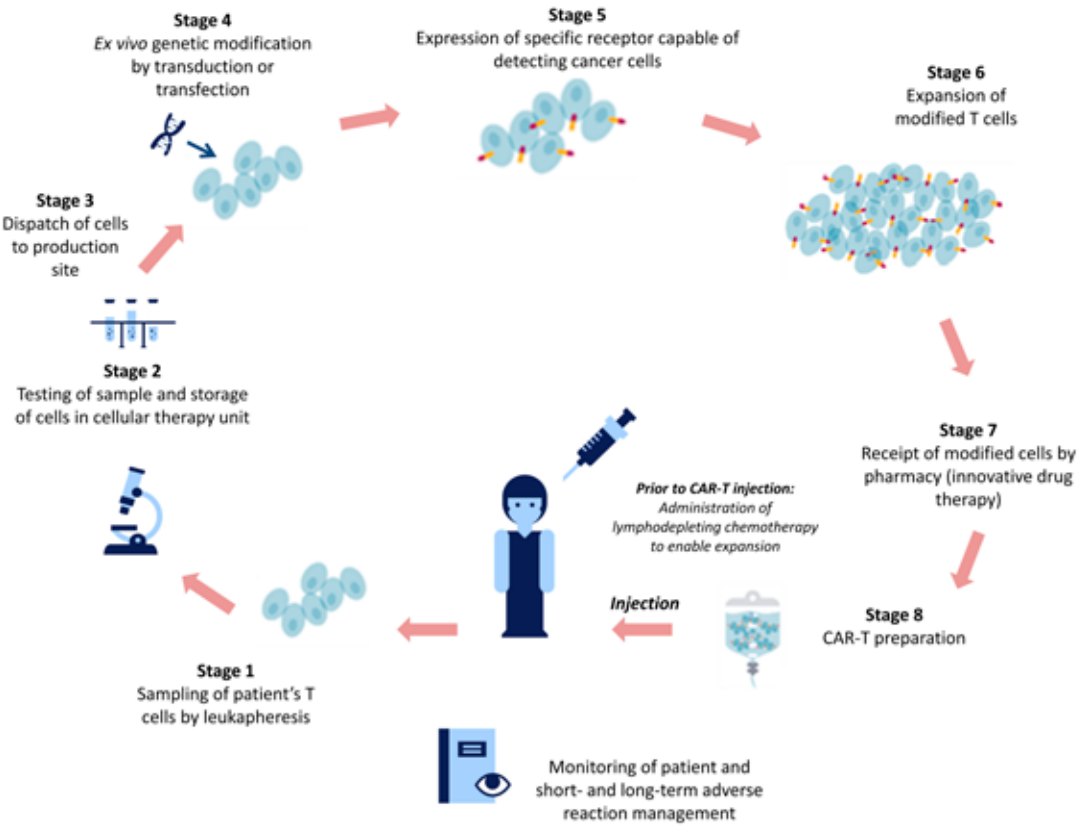
REGISTRATION IN THE SUPPLEMENTARY LIST

At the present time, all the therapeutic indications examined by HAS are registered in the supplementary list, with the exception of nivolumab in the treatment of Hodgkin's disease and in squamous head and neck carcinoma, as well as pembrolizumab in the treatment of urothelial carcinoma for patients ineligible for platinum salts. Note that ipilimumab has been withdrawn from the supplementary list since 1st March 2018 for its indication in adult melanoma following a Transparency Commission review of the SMR and ASMR in 2017.

CAR-T CELLS: A COMPLEX CIRCUIT

The production process and circuit of these drugs, illustrated in the figure below, are complex. The arrival of CAR-T cells in France will make it necessary to address the issue of the restriction of their use to some specialised centres.

FIGURE 2: Main stages of autologous CAR-T cell treatment



Source INCa

SUSTAINABILITY OF COSTS

HIGH PRICES

Only three of the first specific immunotherapies approved in the European Union currently have a defined price available in France. As stezolizumab and avelumab were granted their MA more recently, their price has not yet been determined. As an indication, a sum of over 15,000 should be envisaged for twelve weeks of treatment with an anti-PD-1 monotherapy for a 70 kg patient.

For CAR-T, in the United States, the price of an injection of tisagenlecleucel would be 475,000 USD (32) and of axicabtagene ciloleucel would be 373,000 USD (33). This means that it will be necessary to anticipate the funding methods of such drugs when they have been approved in France.

COSTS ASSOCIATED WITH CHECKPOINT INHIBITORS

The costs associated with checkpoint inhibitors are changing very rapidly: reflecting the increase in the number of therapeutic indications approved for checkpoint inhibitors, the costs associated with ipilimumab, nivolumab and pembrolizumab almost tripled in one year, from 120 million in 2015 to over 340 million in 2016 (ATIH data).

Moreover, the costs are rising due to the long-term regimen for most of the drugs (until disease progression or unacceptable toxicity). The development of specific immunotherapy associations is a further factor liable to contribute to rising costs. Molecular tests may also give rise to an increase in the total costs.

MAJOR ECONOMIC CHALLENGES

Phase III clinical developments of checkpoint inhibitors in multiple tumour sites, increasingly in association with no determined treatment duration, indicate an increase in the costs associated with these drugs.

The arrival of CAR-T cells onto the U.S. market and, in the near future, in the European Union, raises many more questions in relation to the actual cost of such a treatment, in view of the complex circuit of the drug and the ensuing patient care plan. In the United States, the funding of CAR-T cells is the subject of "performance contracts" with the response to treatment applied as the assessment criterion. France is studying the relevance and feasibility of such contracts, the success of which is subject to compiling exhaustive registers, making the right choice in terms of the performance criterion and shared interpretation of the results obtained.

The foreseeable budgetary impact of checkpoint inhibitors and CAR-T cells raises questions on the capability and changes to be envisaged for the French social protection system so as to maintain equitable access to innovation and to the best treatments for all patients.

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- French National Cancer Institute (INCa) website
- European Medicines Agency (EMA) website
- French National Medicines and Health Products Safety Agency (ANSM) website
- French National Authority for Health (HAS) website
- Health Insurance website (AMELI)
- Public medicines database website
- Food and Drug Administration (FDA) website
- French Technical Agency for Information on Hospitalisation (ATIH) website
- French Ministry for Solidarity and Health website (solidarites-sante.gouv.fr)
- Drug Abacus website
- Organization for Economic Cooperation and Development (OECD) website
- Clinical trial registry website Clinicaltrials.gov
- Website of the journal Science

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