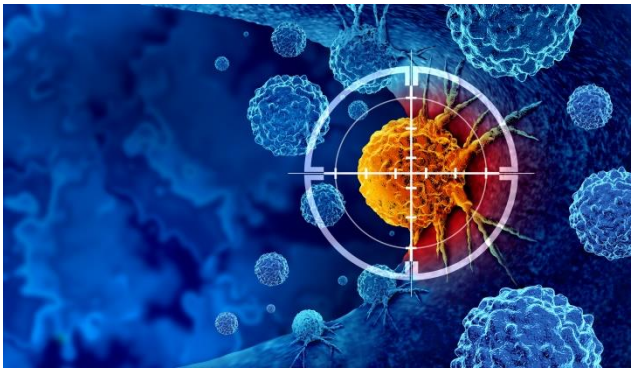
SCIENCE AND TECHNOLOGY BRIEFINGS
PARLIAMENTARY OFFICE FOR SCIENTIFIC AND TECHNOLOGICAL ASSESSMENT

Briefing 40

Therapeutic Advances in Oncology

June 2023

N° 1456 ASSEMBLÉE NATIONALE – N° 809 SÉNAT



freshidea - stock.adobe.com

Summary

- *For several years now, new treatments based on molecular approaches have been supplementing – although not replacing – the therapeutic arsenal used in the fight against cancer.*
- *More precise and effective, these treatments have led to real progress in terms of patient survival and continue to offer significant promise.*
- *The use of personalised treatments is tending to transform cancers into a collection of rare diseases, leading to a significant rise in treatment costs.*

Philippe Berta, Member of the National Assembly
Laure Darcos, Senator

Background

Cancer is one of the leading causes of death worldwide,[1] with 10 million deaths in 2019.[2] This health burden is primarily borne by developed countries where life expectancy is higher.[3] Hence, in 2018, there were 382,000 new cases and 157,400 deaths from the disease in Metropolitan France, making cancer the leading cause of premature mortality, ahead of cardiovascular diseases.[4]

The corresponding economic burden is substantial. For France in 2017, the cost of care was €16.5 billion and the total cost (including loss of production, prevention policies, etc.) was €18.3 billion, up 48% compared to 2004.[5]

Importance of prevention and diagnosis

Therapeutic advances in recent years have led to real progress in terms of patient survival and quality of life, but curative treatment is only one of the levers for reducing the health and social impact of cancer.

In fact, a large proportion of these diseases are lifestyle-related[6] and it is estimated that some 40% of cancers in France could be avoided, in particular the 19.8% related to smoking (68,000 new cases per year) and the 8% related to alcohol (28,000 new cases per year).[4] Similarly, early diagnosis can substantially improve patients' chances of recovery.[7]

Consequently, methods of prevention and diagnosis, which are not covered in this briefing, are essential components in the fight against cancer and must be the subject of ambitious research and public policies.

Traditional treatments

Traditionally, the oncological treatment of solid tumours has been based on surgery to remove the tumour, as well as chemotherapy and radiotherapy to eliminate cancerous cells.

While this therapeutic arsenal has been expanded in recent years, with the addition of new therapies based on molecular approaches, conventional treatments still play a central role in cancer care today. In 2020, surgery, chemotherapy and radiotherapy were used for 395,300, 347,400 and 227,352 patients respectively (compared with only 51,684 patients treated with immune checkpoint inhibitors and 234 patients treated with CAR-T cells).[4]

These traditional techniques are themselves undergoing numerous developments to improve their efficacy while at the same time reducing their side effects.[8] Developments in the field of laparoscopy and thoracoscopy, the use of fluorescent tumour markers and, more recently, robotic assistance have made it possible to perform less invasive surgical procedures, thereby reducing the risk of complications associated with iatrogenic injury. As a result, it is now possible to operate on tumours that were previously inoperable (in particular, spinal cord tumours). Improvements in the precision of radiation and advances in the field of dosimetry have also led to fine-tuning of radiotherapy treatments. In addition, techniques such as proton

therapy, which uses a beam of protons, or brachytherapy, in which the radiation is diffused internally, enable tumour tissue to be eliminated more effectively while preserving the surrounding healthy tissue.[9]

New therapies

In recent years, a better understanding of cancers on a molecular level has resulted in the emergence of "precision medicine", based on personalised treatment using new therapies tailored to the specific abnormalities encountered in individual patients.

This new approach has led to a paradigm shift: the disease is no longer characterised by the location of the tumour, but by its molecular characteristics, and a large number of cancer subtypes can exist for the same organ.[10] Therefore, diagnostic tests, based on tumour biopsies or circulating tumour cells, are required to identify the molecular changes present and guide the treatment prescription.[11]

- **Targeted therapies**

To begin with, targeted therapies were developed to block the growth or spread of the tumour, by acting at the source of the development or dissemination of cancer cells. The differences between healthy cells and cancer cells mean that the latter can be specifically targeted, minimising side effects.

Small inhibitory molecules, which can bind to specific proteins to stop or modify their function and thus block tumour progression, can be used. This is the case, for example, with tyrosine kinase inhibitors; by inhibiting these enzymes that play an essential role in cell signalling, the proliferation of certain cancer cell lines can be blocked.[12]

It is also possible to use antibodies which, by recognising the specific antigens of tumour cells,[13] can block the biological mechanisms involved in their multiplication[14] or trigger their lysis as a result of complement-dependent cytotoxicity (CDC) or antibody-dependent cellular cytotoxicity (ADCC).[15] They can also be used "armed", i.e. linked to one or more cytotoxic products (chemotherapy or radiotherapy drugs), which they selectively direct against cancer cells.[16] This method enables the use of drugs that would be too toxic if administered via conventional systemic chemotherapy.

Although numerous research projects are ongoing and there is still enthusiasm for these approaches, the results are currently fragmented. First of all, the majority of cancers cannot be treated with targeted therapy, due to the absence of a decisive molecular abnormality that could constitute a therapeutic target. Furthermore, while these treatments are effective in terms of reducing the progression of the disease, only a fraction of them improve the overall survival rate of patients, due to the emergence of resistance phenomena in the short or medium term. Finally, the heterogeneity of tumours is a major obstacle: tumour cells are not all identical and, consequently, may respond differently to treatment.[17]

- **Immunotherapies**

To form a tumour, cancer cells have to evade the immune system's defences. The objective of immunotherapy treatments is to restore the immune system's efficiency so that it can recognise and destroy these cells.[18]

In recent years, this approach has made it possible to considerably extend the survival of patients for whom there was no effective treatment,[19] in particular providing benefits in terms of long-term survival, something that is rarer with targeted therapies. Immunotherapies are undeniably the most dynamic and promising area of research in the field of oncology, with more than 6,000 clinical trials currently underway.[20]

- Immune checkpoint inhibitor (ICI) therapy and multispecific antibodies

While antibodies can be used as targeted therapies, they can also be used as immunotherapies, to activate the immune system. It is as immune checkpoint inhibitors that antibodies have revolutionised the field of immunotherapy in recent years.[21]

Immune checkpoints are proteins on the surface of T lymphocytes that prevent the immune system from attacking cells. However, cancer cells hijack this control mechanism to make themselves invisible to the body's defences; they produce molecules on their surface that can bind to the immune checkpoints of lymphocytes, thereby inhibiting the immune system's response. The aim of immune checkpoint inhibitors is to block this mechanism so that T lymphocytes can destroy the tumour cells.[22]

Regardless of the tumour histology, the efficacy of this type of treatment is influenced by several biological parameters: presence of lymphocytic infiltrates in the tumour, expression of the targeted receptor, tumour microenvironment, etc.[23] Although only a fraction of patients respond to these treatments (around 30% on average, with wide variations depending on the type of cancer), the response is generally long-lasting and can lead to cures at the metastatic stage.

Since the first marketing authorisation in 2011, immune checkpoint inhibitors have undergone significant development.[24] Anti-PD1/PDL1 antibodies,[25] such as nivolumab (Opdivo, BMS) or pembrolizumab (Keytruda, MSD),[26] are now used for more than twenty different indications and continue to be subject of extensive research.[27] In particular, promising new results could be obtained by using them as a neo-adjuvant treatment

(before surgery). In addition, numerous studies are seeking to identify new receptors that could be targeted by this type of therapy.[28]

Another type of immunotherapy is based on the use of multispecific antibodies, i.e. antibodies that have several binding sites. They can therefore bind simultaneously to immune system cells (T lymphocytes or NK cells) and cancer cells, promoting the latter's destruction.[29] This approach makes it possible to target several tumour antigens (using trispecific or even quadrispecific antibodies) and therefore overcome the heterogeneity of tumour cells.[30]

- Cell therapies

Chimeric antigen receptor T cell (CAR-T) therapy involves harvesting, modifying and using a patient's own T cells to treat their cancer. The lymphocytes are genetically modified to produce receptors that recognise cancer cell antigens and are then reinjected into the patient.[31]

Despite side effects that can be significant following injection,[32] this strategy is particularly effective for the treatment of blood cancers (leukaemia, lymphoma, myeloma). However, as an autologous treatment,[33] this approach is costly, with limited production capacities. While a number of studies are underway to improve the production process, by dispensing with the need for viruses modifying the T cells genetically, or even attempting to modify T cells in vivo using gene therapy, the ideal solution would be to develop an allogeneic treatment.[34] However, as research currently stands, this remains a long-term objective, since allogeneic cells are eliminated rapidly by the body.[35]

The use of this approach for solid tumours is also hampered by the absence of an ideal tumour marker – i.e. one that is sufficiently expressed by tumour cells without being expressed by healthy cells[36] –, the heterogeneity of these tumours, their physico-chemically disrupted microenvironment, which prevents the action of the T cells, and the difficulty of accessing tumour cells. However, tumour-infiltrating lymphocyte (TIL) therapy can help to achieve results, by injecting, following their multiplication, lymphocytes capable of naturally detecting the tumour's specific mutations, obtained from a biopsy.

- Vaccines

The immune response can be stimulated and directed against cancer cells by curative vaccines,[37] by administering tumour antigens (or molecules coding for them, such as messenger RNAs).

While the first approaches using shared antigens (found in several patients) were unsuccessful for a long time,[38] new approaches using "private" antigens (or neo-antigens, specific to each patient's tumour) are now showing more promising results. This prospect is now becoming a realistic one thanks to advances in sequencing techniques, making it possible to identify patient-specific mutations, as well as improved production processes, making it possible to produce a personalised vaccine within a reasonable timeframe. Encouraging results have recently been obtained with mRNA vaccines, which inject genetic material that is then translated into tumour proteins.[39] By inducing the production of cytotoxic T lymphocytes, vaccination could prove to be particularly effective in combination with immune checkpoint inhibitors, which only work in the presence of a sufficiently large intra-tumour lymphocyte infiltrate. However, as with CAR-T cells, this type of personalised strategy involves significant treatment costs.

In the longer term, recent discoveries pave the way for the possibility of more universal vaccination.[40] In cancer cells, transposons (or "jumping genes"), which are generally silent, are reactivated, leading to the production of aberrant proteins. The antigens expressed in this way, which are absent from healthy cells and common to various forms of cancer, could be ideal targets for a pan-cancer vaccine.

Position of French research

Between 2015 and 2019, France was ranked seventh in the world in terms of number of publications in the field of oncology research.[41] Having participated in around 10% of the interventional cancer studies conducted worldwide in 2019, it was ranked third on this criterion, behind China and the United States.

As with the rest of French research in the fields of biology and health, a decline has been observed in recent years, primarily due to under-funding of research compared with the best international standards.[42] For clinical trials, despite recent improvements, France's attractiveness continues to suffer from the fact that the time-frames for setting up trials are perceived as being excessively long.[43]

Accessibility and price of treatments

- **Accessibility**

Although the time between granting of a marketing authorisation and inclusion on the list of reimbursable medicines is relatively long in France,[44] the early access mechanism gives French patients quick access to treatments considered to be particularly innovative.[45]

However, the French Societal Cancer Observatory highlights the fact that there are major inequalities in access to treatments, including the most innovative ones, thereby accentuating existing social and geographical healthcare inequalities.[46] Problems with access to certain diagnostic tests can also be highlighted, with this preventing the use of personalised

medicines, along with shortages of certain essential medicines.[47]

Without calling into question the quality requirements applicable to the assessment of new therapies,[48] several of the people interviewed felt that the French National Authority for Health (HAS) doctrine was inappropriate for certain new treatments.[49] For example, the rarity of certain targeted mutations makes it difficult to set up large-scale randomised trials. In addition, in cases where the first phases of clinical trials demonstrate exceptional results against forms of cancer with a poor prognosis, the use of a control arm in the subsequent phases may be perceived as unethical because of the resulting loss of opportunity for the patients enrolled in this arm.

- **Price**

Compared with traditional therapies, the price of innovative treatments is often much higher (up to several hundred thousand euros per patient) due to the R&D work required, sometimes higher production costs, and smaller markets in the case of personalised treatments.[43,50] Hence, according to the French National Health Insurance system, the average cost of a year of life gained rose from €15,877 in 1996 to €175,968 in 2016.[51]

In the future, this trend is likely to have an impact on the financial equilibrium of the social welfare system and raise questions about equity of access to the best treatments available.

Recommendations

- Provide financial support for the development of innovative treatments in France,[52] from fundamental research through to industrial development, and encourage the establishment of public-private partnerships.
- Reinforce the role of the French National Cancer Institute (INCa) in programming and coordinating cancer research and use it as a model to streamline the organisation of public research in the fields of biology and health.
- Develop the availability of diagnostic tests, essential for precision medicine, and enable them to be reimbursed. Increase the number of genomics platforms by using public-private partnerships.
- Enable clinical trials to be set up more quickly, in order to boost France's attractiveness for research, in particular by offering new resources to Committees for the protection of persons (CPP).
- Invite the French National Authority for Health (HAS) to adapt its assessment models for innovative treatments.
- Increase the number of genetic counsellors, bioinformaticians and clinical research associates in hospitals, by enlisting people from scientific backgrounds.
- Reform the French national health insurance expenditure target (ONDAM) to enable long-term management of spending on innovative medicines.
- Involve researchers, patient associations, physicians and industrial players in decision-making wherever possible.

The Office's websites:
http://www.assemblee-nationale.fr/commissions/opecst-index.asp
http://www.senat.fr/opecst

Persons consulted

Norbert Ifrah, President of the French National Cancer Institute (INCa)

Manuel Rodrigues, President of the French Cancer Society

Daniel Nizri, President of the French Cancer League

Patrick Chames, Research Director at the CNRS, in charge of the "Therapeutic antibodies and immune-targeting" research team at the Marseille cancer research centre

Maha Ayyoub, University Professor and Hospital Practitioner at the Toulouse-Oncopole University Cancer Institute and Paul Sabatier University, research director in charge of the "Anti-cancer immunity and immunotherapy" research team at the Toulouse cancer research centre

Hervé Brailly, chair of the Innate Pharma supervisory board

Jean-Yves Blay, President of Unicancer, Sophie Beaupère, Managing Director of Unicancer, and Muriel Dahan, Research and Development Director at Unicancer

Marion Alcantara, President of the French Cancer Immunotherapy Society

Eric Quéméneur, Executive Vice-President in charge of research and development at Transgene

Aurélien Marabelle, University Professor and Hospital Practitioner at the Gustave-Roussy Institute, responsible for the "Translational research in immunology laboratory"

Christian Deleuze, Deputy Managing Director for Innovation at Sanofi, Marielle Chiron, Director of the Sanofi immuno-oncology research centre, and Cécile Orsini, senior scientist at Sanofi

Caroline Robert, University Professor and Hospital Practitioner at the Gustave-Roussy Institute, head of the Department of Dermatology and director of the "Adaptive resistance to cancer therapies" research team

Bernard Pau, President of Mabqi

Références

[1] G. A. Roth *et al.*, *Lancet* 2018, 392, 1736 (https://doi.org/10.1016/S0140-6736(18)32203-7).

[2] GBD 2019 Diseases and Injuries Collaborators, *Lancet* 2020, 396, 1204 (https://doi.org/10.1016/S0140-6736(20)30925-9).

[3] H. Sung *et al.*, *CA Cancer J. Clin.* 2021, 71, 209 (https://doi.org/10.3322/caac.21660).

[4] INCa, "*Panorama des cancers en France*", 2022 (https://www.e-cancer.fr/Expertises-et-publications/Catalogue-des-publications/Panorama-des-cancers-en-France-Edition-2022).

[5] The rise observed is primarily due to an increased incidence. See: Asteres, "*Le coût du cancer en France : une forte hausse*", 2020 (https://asteres.fr/site/wp-content/uploads/2020/02/ASTERES-CANCER-FEV-2020-compresse.pdf).

[6] G. Danaei *et al.*, *Lancet* 2005, 366, 1784 (https://doi.org/10.1016/S0140-6736(05)67725-2).

[7] a) H. Cho *et al.*, *J. Natl. Cancer Inst. Monogr.* 2014, 49, 187 (https://doi.org/10.1093/jncimonographs/lgu014); b) A. M. Aravanis *et al.*, *Cell* 2017, 168, 571 (https://doi.org/10.1016/j.cell.2017.01.030); c) A. K. Mattox *et al.*, *Sci. Transl. Med.* 2019, 11, eaay19 (https://doi.org/10.1126/scitranslmed.aay1984). For example, it has been estimated that delays in diagnosis and treatment due to the first wave of Covid-19 (between March and July 2020) could result in between 1,000 and 6,000 additional cancer deaths in France over the next few years. See: J.-Y. Blay *et al.*, *ESMO Open* 2021, 6, 100134 (https://doi.org/10.1016/j.esmoop.2021.100134).

[8] Improvements in imaging techniques have also enabled more targeted interventions thanks to more precise definition of the tumour location and volume. The development of new destructive treatments, using ultrasound, radiofrequency, lasers, microwaves or cryotherapy, which can be used as complementary or alternative therapies, should also be highlighted.

[9] In the case of conventional X-ray radiotherapy, secondary cancers develop in around 5% of patients. See: C. B. Dracham *et al.*, *Radiat. Oncol. J.* 2018, 36, 85 (https://doi.org/10.3857%2Froj.2018.00290). However, these techniques have to contend with a limited number of devices and trained specialists. See: J.-M. Hannoun-Lévi *et al.*, *Cancer Radiother.* 2020, 24, 876 (https://doi.org/10.1016/j.canrad.2020.03.010).

[10] Conversely, the same abnormality may be found in cancers affecting different organs. This is the case, for example, for alterations affecting the NTRK gene (coding for the TRK receptor), enabling the use of therapies that target this receptor and have been shown to be effective irrespective of the organ involved. See: E. Cocco *et al.*, *Nat. Rev. Clin. Oncol.* 2018, 15, 731 (https://doi.org/10.1038/s41571-018-0113-0).

[11] E. R. Malone *et al.*, *Genome Med.* 2020, 12, 8 (E. R. Malone et al., Genome Med. 2020, 12, 8). Recently, a team of French researchers introduced the concept of "induced volatolomics", which involves using tumour-activatable probes to identify tumour markers from expired tracers. See: R. Châtre *et al.*, *Chem. Sci.* 2023, 14, 4697 (https://doi.org/10.1039/D2SC06797H).

[12] C. Pottier *et al.*, *Cancers* 2020, 12, 731 (https://doi.org/10.3390/cancers12030731).

[13] In addition to targeting antigens specific to tumour cells, the design of antibodies whose binding affinity depends on pH makes it possible to selectively target tumour cells, which have a more acidic environment. See: T. Klaus *et al.*, *J. Biomed. Sci.* 2021, 28, 11 (https://doi.org/10.1186/s12929-021-00709-7).

[14] D. Zahavi *et al.*, *Antibodies* 2020, 9, 34; (https://doi.org/10.3390/antib9030034).

[15] G. J. Weiner, *Nat. Rev. Cancer* 2015, 15, 361 (https://doi.org/10.1038/nrc3930).

[16] The use of "armed" antibodies results in observation of a "bystander" effect: once the cell has been destroyed, the cytotoxic drug is released and can destroy neighbouring cells. This mechanism partially counteracts tumour heterogeneity, since neighbouring cells do not necessarily express the targeted receptor.

[17] A. Marusyk *et al.*, *Biochim. Biophys. Acta Rev. Cancer* 2010, 1805, 105 (https://doi.org/10.1016/j.bbcan.2009.11.002).

[18] At the end of the 19th century, Dr William B. Coley had already observed that stimulating the immune system by inoculating it with bacterial strains led to tumour regression. See: G. S. Kienle *et al.*, *Glob. Adv. Health Med.* 2012, 1, 92 (https://doi.org/10.7453%2Fgahmj.2012.1.1.016).

[19] A. D. Waldman *et al.*, *Nat. Rev. Immunol.* 2020 20, 651 (https://doi.org/10.1038/s41577-020-0306-5).

[20] https://clinicaltrials.gov/

[21] R.-M. Lu *et al.*, *J. Biomed. Sci.* 2020, 27, 1 (https://doi.org/10.1186/s12929-019-0592-z).

[22] This discovery won James P. Allison and Tasuku Honjo the Nobel prize for medicine in 2018.

[23] R. Bai *et al.*, *Biomark Res.* 2020, 8, 34 (https://doi.org/10.1186/s40364-020-00209-0).

[24] R. Zaim et al., *J. Cancer Policy* 2022, 33, 100346 (https://doi.org/10.1016/j.jcpo.2022.100346).

[25] It is possible to act on the PD1 (programmed cell death protein 1) receptor present on T lymphocytes or on the PDL1 (programmed death-ligand 1) receptor present on tumour cells. The majority of checkpoint inhibitors on the market target this pair of receptors.

[26] Pembrolizumab is set to become the world's most lucrative medicinal product, with sales expected to exceed $20 billion by 2023, compared with around $10 billion for nivolumab. See: A. Brown *et al.*, "*Evaluate Vantage 2023 Preview*" 2022 (https://info.evaluate.com/rs/607-YGS-364/images/Vantage%20Preview%20Report%202023.pdf).

[27] a) L. Hirsch *et al.*, *Br. J. Cancer* 2019, 120, 3 (https://doi.org/10.1038/s41416-018-0294-4); b) S. Upadhaya *et al.*, *Nat. Rev. Drug Discov. 2021,* 20, 503 (https://doi.org/10.1038/d41573-021-00100-z).

[28] S. Jeong et al., *Immune Netw.* 2020, 20, e3 (https://doi.org/10.4110/in.2020.20.e3).

[29] H. G. Shin *et al.*, *Int. J. Mol. Sci.* 2022, 23, 5686 (https://doi.org/10.3390/ijms23105686).

[30] However, the increase in the number of antigens targeted also increases the risk of triggering an autoimmune reaction.

[31] A. N. Miliotou *et al.*, *Curr. Pharm. Biotechnol.* 2018, 19, 5 (https://doi.org/10.2174/1389201019666180418095526).

[32] During the first injection, there is a high risk of cytokine release syndrome, which may lead to cytokine shock. See: D. Porter *et al.*, *J. Hematol. Oncol.* 2018, 11, 35 (https://doi.org/10.1186/s13045-018-0571-y).

[33] The T cell donor and recipient being the same person.

[34] J. Zhao *et al.*, *J. Hematol. Oncol.* 2018, 11, 132 (https://doi.org/10.1186/s13045-018-0677-2).

[35] Allogeneic CAR-NKs have been developed, but their persistence is poor at present. See: S. Nguyen *et al.*, *Bull. Cancer* 2021, 108, S81 (https://doi-org.insb.bib.cnrs.fr/10.1016/j.bulcan.2021.06.007).

[36] The markers targeted in the case of blood cancers (CD19 and CD20) are also only expressed by B cells, which are not essential and are regenerated following treatment.

[37] These vaccines are used to treat the cancer and not to prevent it, as is the case with prophylactic vaccines used in infectious diseases.

[38] Patients with the same tumour share less than 10% of common antigens.

[39] Clinical trials are being conducted on melanoma and colorectal cancer, in particular, by BioNTech, Moderna and Gritstone. In France, a recombinant vector vaccine developed by Transgene, is expected to enter phase 2 trials in 2023.

[40] N. M. Shah *et al.*, Nat. Genet. 2023, 55, 631(https://doi.org/10.1038/s41588-023-01349-3).

[41] CNCR, FHF Cancer, "*Quelle est la place de la France en recherche en cancérologie ?*", 2021 (https://cncr.fr/wp-content/uploads/2021/06/CNCR-FHF_LaRechercheEnCancerologie_vf.pdf).

[42] "*Le financement et l'organisation de la recherche en biologie*-santé", Report by Messrs Gérard Longuet, Senator, and Cédric Villani, Member of the National Assembly, conducted on behalf of the Parliamentary Office for Scientific and Technological Assessment (OPECST), submitted on 15 July 2021- National Assembly No. 4373 (15th legislative term), Senate No. 770 (2020-2021) (https://www.senat.fr/rap/r20-770/r20-770.html). Between 1980 and 1984, France was ranked fifth in the world in terms of number of publications in the field of oncology research (see previous reference).

[43] Report No. 4275 (15th legislative term) by Ms Audrey Dufeu and Mr Jean-Louis Touraine, Members of the National Assembly, concluding the work of the fact-finding mission on medicinal products (https://www.assemblee-nationale.fr/dyn/15/rapports/cion-soc/l15b4275_rapport-information.pdf).

[44] This time-frame was 490 days between 2017 and 2020, with France ranked 20th out of the 39 countries assessed. See: IQVIA, "*EFPIA Patients W.A.I.T. Indicator 2021 Survey*", 2022 (https://www.efpia.eu/media/676539/efpia-patient-wait-indicator_update-july-2022_final.pdf).

[45] Taking into account the more rapid access provided by the early access mechanism, France was ranked second in terms of access times between 2016 and 2018. See: L. Khalfallah-Neelz, "*Les différents systèmes d'accès au marché en Europe : les inégalités de remboursement et de délais d'accès aux soins d'oncologie entre les pays*", 2022 (https://dumas.ccsd.cnrs.fr/dumas-03930146/document).

[46] Observatoire sociétal des cancers, "*Face au cancer, l'épreuve du parcours de soins – Rapport 2018/2019*", 2019 (https://www.ligue-cancer.net/sites/default/files/docs/observatoire_societal_des_cancers_rapport_2018-2019_0.pdf).

[47] See the Senate committee of enquiry investigating the shortage of medicines and the choices made by the French pharmaceutical industry.

[48] "*Traitements contre le cancer : 'Le bénéfice des nouveaux médicaments, évalué à court terme, est trop incertain'*", Le Monde, 2023 (https://www.lemonde.fr/sciences/article/2023/05/19/traitements-contre-le-cancer-le-benefice-des-nouveaux-medicaments-evalue-a-court-terme-est-trop-incertain_6173985_1650684.html).

[49] Z. Chaffin, "*Ces médicaments innovants qui ne sont pas disponibles en France pour soigner les patients*", *Le Monde* 2023 (https://www.lemonde.fr/economie/article/2023/06/04/ces-medicaments-innovants-qui-ne-sont-pas-disponibles-en-france-pour-soigner-les-patients_6176149_3234.html). However, progress has recently been made, with the new HAS Transparency Committee (CT) doctrine allowing a clinical added value (ASMR) to be recognised even in the event of an indirect comparisons, if justified and methodologically robust. See: A. Vanier *et al.*, *BMJ Evid.-Based Med.* 2023, *in press* (http://dx.doi.org/10.1136/bmjebm-2022-112091).

[50] C. Saout, C. Pajares y Sanchez, "*Prix et accès aux traitements médicamenteux innovants*", 2017 (https://www.lecese.fr/travaux-publies/prix-et-acces-aux-medicaments-innovants).

[51] *Caisse nationale de l'assurance maladie* [French national health insurance fund], "*Améliorer la qualité du système de santé et maîtriser les dépenses : les propositions de l'Assurance Maladie pour 2018*", 2017 (https://assurance-maladie.ameli.fr/etudes-et-donnees/2017-rapport-propositions-pour-2018-charges-produits).

[52] Research and development spending must reach and exceed 3% of gross domestic product, the target set by the "Lisbon Strategy" adopted in 2000.