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Original Research

Comparative study on anticancer drug access times between FDA, EMA and the French temporary authorisation for use program over 13 years

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Abstract ***Introduction:*** The cancer incidence continues to rise worldwide. Medical innovation has a major impact on patient survival, but within drug development, it can take more than 10 years to obtain marketing authorisation (MA). The time required for access to therapeutic innovation remains critical, so France has developed a specific expanded access program named ATU, which allows the administration of drugs before the European Medicines Agency (EMA) approval. The purpose of this study is to put in perspective the average time to access antineoplastic drugs worldwide, taking into account ATU, US Food and Drug Administration (FDA) and EMA approvals.

Methods: The ATU system allows the use of a medicine before its MA, under exceptional conditions. All antineoplastic drugs in oncology that have benefited from the ATU system are analysed in terms of tumour site, biomarkers and number of patients who have access to the drug.

Results: Between 1st January 2007 and 31st December 2019, 36 of 64 drugs (56.2%) that received MA in oncology were assigned an ATU, to the benefit of 16,927 patients. Thanks

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to the ATU, 25 of 36 drugs (69.4%) were made available early, on average 203 d (95% CI, 76–330) before FDA approval and on average 428 d (95% CI, 272–583) before EMA approval. Only three of 36 drugs were approved by the EMA before the FDA, and the average time lapse between European MA and FDA approval for these 36 drugs was 216 d (95% CI, 140–293).

Conclusion: This article demonstrates that the ATU system allows patients to benefit from therapeutic innovations before MA in Europe and USA, with full coverage by the healthcare system.

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1. Introduction

The cancer incidence continues to rise worldwide. There were about 18,000,000 new cases in 2018 and about 9,500,000 deaths. Despite therapeutic advances, cancer has become the leading cause of death since 2004 in France, with 157,000 deaths in 2018 [1,2]. To cope with this challenge, societies need to adapt their approach to cancer prevention and treatment, with changes in the development and use of innovative antineoplastic drugs playing an important role. Medical innovation has a major impact on patient survival and longevity. The joint assessment of incidence, mortality and survival shows that real progress has been made in the management of many cancers. Overall, patient survival continues to increase, although there is a wide disparity between countries. Although few studies have addressed the issue because of the many variables and confounding factors, the time required for access to treatment appears to have an impact on survival [3,4].

In the development of a drug, from the laboratory research phase to the end of clinical trials, it can take more than 10 years to obtain marketing authorisation (MA). The MA should guarantee the quality, efficacy and safety of the product. In addition, there are procedures for access to the medicinal products market before the marketing of the medicinal product is possible. Access to cancer drugs, especially new innovative drugs, varies worldwide and depends on the country's economic strength and policy choices based on scientific evidence and cost-effectiveness. In the European Union (EU), access to new cancer drugs involves centralised licensing decisions by regulators and then each country decides on repayment according to its national healthcare systems. The Committee for Medicinal Products for Human Use of the European Medicines Agency (EMA) carries out a scientific assessment of the application and gives a recommendation on whether the medicine should be marketed or not. However, under EU law, EMA has no authority to permit marketing in the different EU countries. The European Commission is the authorising body for all centrally authorised products, and it takes a legally binding decision based on EMA's recommendation. Once granted by the European Commission, the centralised MA is valid in all EU Member States as well as in the following European Economic Area countries: Iceland, Liechtenstein and Norway [5].

In France, the average time between MA and patient access to reimbursable drugs is 530 d [6], which has led to numerous criticisms about delays in access to therapeutic innovation compared to other European countries or those worldwide such as the United States of America (USA). However, these criticisms do not take into account the early availability of medicines, well before MA and reimbursement, via expanded access. Expanded access, known in France as *Autorisation temporaire d'utilisation* (ATU), makes it possible to use, on an exceptional basis and over a limited but potentially renewable period, a pharmaceutical speciality that does not have an MA and is not available to patients through a clinical trial. The purpose of this study is to analyse the average time for access to antineoplastic treatments, taking into account ATU, in relation to the date of US Food and Drug Administration (FDA) and EMA approval.

2. Methods

2.1. Particularities of the ATU system

ATU was implemented in 1994. The exceptional use of a medicinal product before its MA is subject to an authorisation for use granted by the French National Agency for the Safety of Medicines and Health Products (ANSM) under the following conditions: specialities are intended to treat, prevent or diagnose serious or rare diseases; there is no appropriate treatment available on the market; their benefit/risk balance in use is presumed to be positive according to the state of scientific knowledge; the implementation of the process cannot be postponed; and the patient cannot obtain the drug through a clinical trial [7,8].

The ANSM may at any time suspend or withdraw these authorisations on public health grounds or if the conditions under which they were granted are no longer

met. Drugs available under an ATU are not available in the city pharmacy, as they do not have an MA. Patients should be allowed to be treated in clinical trials, if they exist, as a matter of priority, as these exceptional authorisations are not intended for investigative purposes but rather to produce real-life data before approval and outside a clinical trial [9].

Currently, ATUs fall under the following three categories: (1) cohort ATU (ATUc), (2) extension ATU (ATUc EI) and (3) nominative ATU (ATUn) (Fig. 1).

These three types of ATU are different both in their modalities and in their place in the life of the future drug:

- The ATUn, issued to a designated patient, on the initiative of the prescribing physician and under his or her responsibility, for a speciality that does not have an MA. The evaluation is carried out on a case-by-case basis by a clinical assessor, based on the clinical information provided by the prescriber and the documents provided by the holder of the exploitation rights. Since 17th September 2019, a one-stop-shop has been available to professionals, aimed at ensuring transparent, rapid and equitable access for all patients throughout the country. The ATUn is issued for a fixed period, which is specified on the authorisation and may not exceed 1 year [10,11].
- The ATUc, issued at the request of the holder of the exploitation rights, for a speciality that does not have an MA, is at an advanced stage of clinical development and concerns only those drugs for which the benefit/risk ratio is presumed to be positive. The pharmaceutical company is required to file an MA application or to undertake to file it within a set time limit.
- The ATUc EI, which allows an ATU to be granted for a drug that already has an MA in a different indication. This system was implemented at the beginning of 2019. To obtain reimbursement via the Social Security, drugs must be prescribed as part of their MA. The ATUc EI actually concern medicines that have received an MA for a specific indication and for which it is desired to extend the indication. At the time when the ATUc EI begins, the medicinal product may under no circumstances be prescribed 'off-label' for the indication covered by the extension.

The evaluation of ATUc applications takes an average of 4 months to complete. The ANSM evaluates the drug for pharmaceutical quality, safety and efficacy. This ATU is valid for 1 year and can be renewed if necessary [12].

As part of the monitoring process and proper use of the drug, when a situation not in conformity with the MA is identified, the ANSM may take the opportunity to develop a temporary recommendation for use (*recommandation temporaire d'utilisation*—RTU) when it identifies an unmet therapeutic need, to regulate prescriptions. The objective is to secure the use of medicines. RTUs are issued for a maximum period of 3 years, which are renewable. As compared with the ATUc EI, the RTU is used when the industrial firm cannot or does not apply for a new MA.

Both ATU and RTU drugs are delivered in hospital pharmacies only.

When a drug obtains an MA, ANSM determines the date on which the ATUc ends or from which it will no longer be possible to obtain the ATU. This date depends on the date of notification of the MA and the time required for the pharmaceutical firm to be able to make the drug available in accordance with its MA. To prevent any disruption in patient care, it is possible to continue delivering drugs that have benefited from an ATU by health establishments, along with Social Security coverage until the reimbursement or publication of its price. This so-called 'post-ATU' phase begins on the date the ATU stops (date of MA) and ends when the price and reimbursement are published in the *Official Journal of the French Republic*.

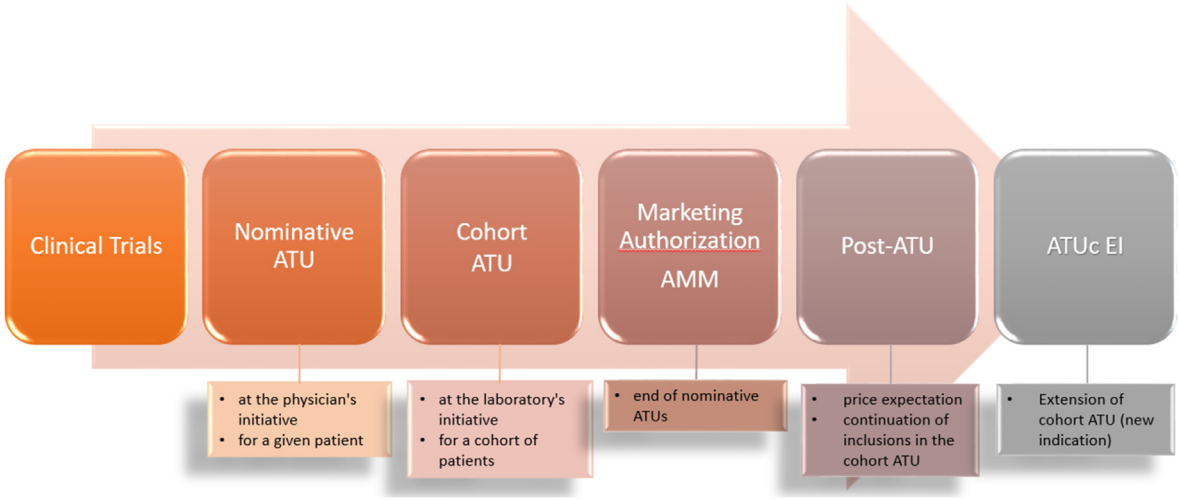

Fig. 1. The availability of drugs in France. AMM, French marketing authorization; ATU, Autorisation temporaire d'utilisation; ATUc EI, extension of cohort ATU.

In France, the price of a drug benefiting from an ATU can be set freely, with no regulation. It is set by pharmaceutical firms without any evaluation by the national authorities. Indeed, this compassionate use system is positioned before the market access procedure by way of exemption from the MA, but also from the evaluation by the French National Authority on Health (HAS) and the price-setting procedure by the independent Economic Committee on Health Products (CEPS). In fact, once MA is obtained, HAS evaluates the drug for reimbursement and pricing. For this purpose, the Transparency Commission (CT) evaluates the medical service rendered (SMR) and the improved medical service rendered (ASMR). When the drug claims to be innovative and may have a significant impact on Social Security expenditure, the HAS Economic Evaluation and Public Health Commission (CEESP) evaluates its efficiency. The National Union of Health Insurance Funds (UNCAM) then sets the reimbursement rate. Finally, the price is negotiated between the CEPS and the pharmaceutical firm based on clinical data and the HAS evaluation [13].

Initially, pharmaceutical firms made these drugs available free of charge. Today, thanks to this tariff freedom, they are permitted to set prices that will serve as a basis for future price negotiations. However, if the price set by the CEPS is lower than the amount previously set by the firm, the firm must pay the difference to the Social Security. Drugs prescribed as part of an ATU, whether nominative or cohort, are fully covered by the Social Security.

This study focused on the quantitative and qualitative expanded access measures (ATUn, ATUc and ATUc EI) and temporary recommendations for use (RTU) evaluated and launched by the ANSM over the last 13 years in oncology. Although the ATU system started in 1994, we focused on the period between January 2007 and December 2019 because before this period, data were very heterogeneous in quality and therefore could not be used.

2.2. Selection of medicines and data sources

Using data from ANSM, all antineoplastic and endocrine medicines in oncology that have benefited from the ATU system and were authorised between 2007 and 2019 were identified. Medicines that were withdrawn post-approval, suspended, or refused by EMA or the ANSM were not included. Generics and biosimilars were excluded. Furthermore, as haematology is a very different speciality to medical oncology and involves different stakes, particularly in terms of analysis of the risk-benefit ratio, antineoplastic drugs in haematology were also excluded. The dates of European MAs for cancer medicines were obtained from the EMA website. Data on the FDA standard approval, expedited approval programs (accelerated approval, breakthrough, fast track and priority review) were extracted from the FDA website and the FDA novel drug summaries.

The time a medicine first becomes available (launch) was defined as the month in which a new medicine was first procured in either hospital or outpatient settings. The date of availability may therefore precede the reimbursement of the drug.

3. Results

Between 1st January 2007 and 31st December 2019, the ANSM evaluated and assigned in oncology an ATU to 36 antineoplastic drugs. Of these drugs, six were immunotherapies (16.7%) and 30 were targeted therapies (83.3%) (see Fig. 2). Except alpelisib for which the case is pending, all these drugs received secondary EMA approval. During the same period, 67 drugs were granted MA in oncology. This means that more than 50% (53.7%) of the medicines that obtained an MA were made available early through the ATU system.

In 13 years, 16,927 French patients were able to benefit from therapeutic innovations for the treatment of their cancer within the framework of an ATU, that is, an average of 1692 patients per year. Among these patients, 5774 were able to benefit from an ATUn and 11,153 from an ATUc (Fig. 3). Forty-three patients (0.2%) were less than 18 years old.

The six drugs with the highest number of patients treated via an ATU were, in order: nivolumab (2660 patients), palbociclib (1774 patients), abiraterone acetate (1629 patients), regorafenib (1205 patients), pembrolizumab (1181 patients) and ipilimumab (988 patients). These results can be explained by the fact that some drugs may have benefited from an ATU in several indications. This is the case for nivolumab, indicated for patients with metastatic melanoma or non–small-cell lung cancer (NSCLC), and regorafenib, indicated for patients with metastatic colorectal adenocarcinoma or gastrointestinal stromal tumours. For the other drugs, this is due to the high prevalence of the target population (patients with HR + metastatic breast cancer for palbociclib, those with castration-resistant metastatic prostate cancer for abiraterone acetate) and/or a lack of other effective therapeutic opportunities (patients with metastatic or locally advanced melanoma for pembrolizumab and ipilimumab).

Twenty-six percent of the treatments that were made available early in the context of ATU have an indication in the treatment of skin cancers (of which 20% in melanoma) and 20% in NSCLC. Among these ATU drugs, the most represented classes are immunotherapies (17%) and targeted therapies acting on the ALK (14%) and PARP (12%) (Supplemental figure 1).

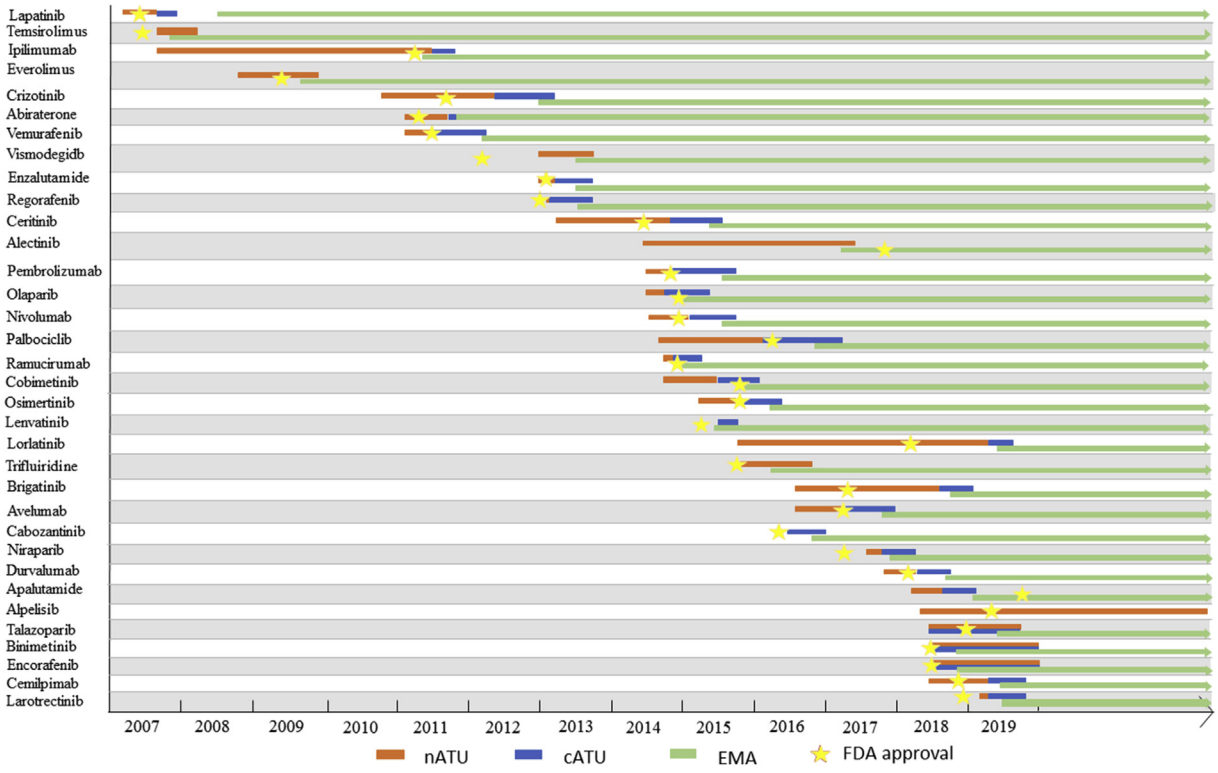

Fig. 2. Neoplastic drugs have benefited from the ATU system and were authorised between 2010 and 2019 in France.

We then looked at the timeframes for making the 36 drugs that benefited from an ATU available in the USA, Europe and France. Although the average time lapse between European MA and FDA approval for these 36 drugs is 216 d (95% confidence interval [CI] 140–293), thanks to ATUs, the antineoplastic drugs were made available in France on average 203 d (95% CI 76–330) before their approval by the FDA in the USA and on average 428 d (95% CI 272–583) before EMA approval. The mean time from onset to completion of ATUs (nominative and/or cohort) was 420 d (95% CI 365–673) (Fig. 4). Thanks to ATUs, 25 of the 36 (69.4%) drugs were made available early, even before FDA approval. Only eleven drugs (30.6%) had access

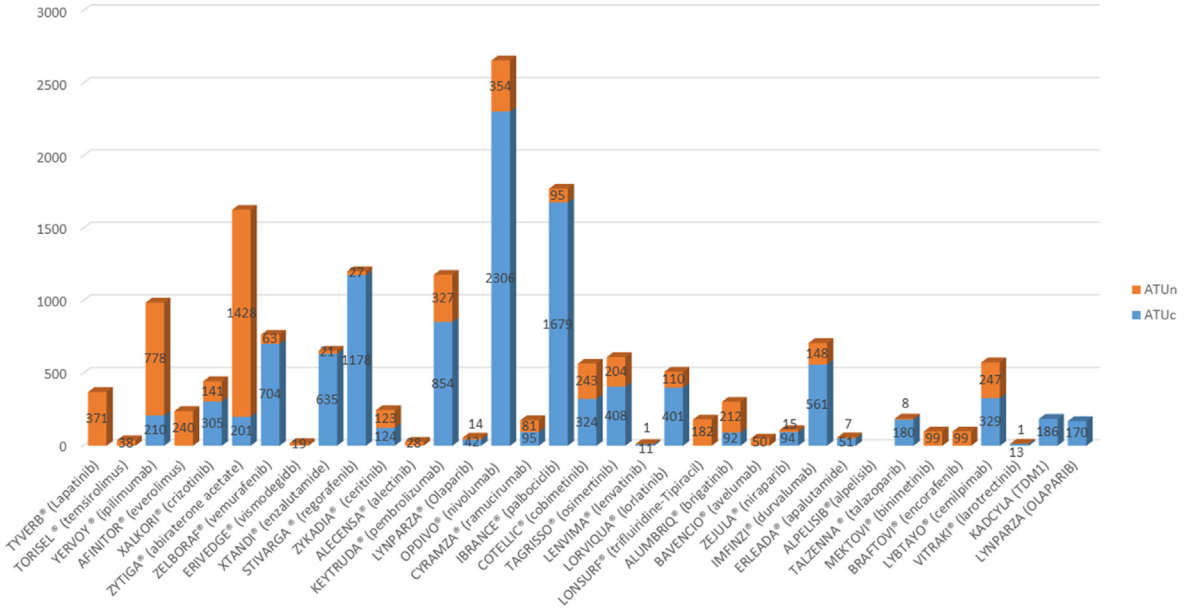

Fig. 3. Detail by molecule of the number of patients included in ATUc or having benefited from an ATUn between 1st January 2007 and 31st December 2019. ATUn, nominative ATU.

after FDA approval. All medicines had early access before EMA approval. The EMA almost systematically gave access to medicines after the FDA, as only three medicines (8.3%) were approved by the EMA before the FDA.

Some drugs were also approved by the FDA for indications other than those approved by the EMA. For example, nivolumab (in combination with ipilimumab, based on the phase II CHECKMATE-142 study) and pembrolizumab were approved by the FDA for the treatment of pre-treated, microsatellite instability-high or deficient mismatch repair, metastatic colorectal cancer, which was not the case in Europe. Finally, larotrectinib is, to date, the only drug that has been granted MA in Europe and the USA for patients with NTRK-fused tumours, regardless of the location of the primary tumour.

4. Discussion

Cancer is one of the greatest public health problems in the world. To fight this scourge, improving the development of anticancer drugs and the efficiency of health systems is a top priority. More effective antineoplastic treatments must reach patients in a timely fashion and at affordable prices. Several processes have been developed by the FDA and EMA to help ensure early access to promising drugs: fast track FDA, prime EMA, priority review FDA, accelerated approval FDA, breakthrough therapy FDA and conditional approval EMA. Unfortunately, given the complexity and time-consuming nature of these regulatory processes, early access to anticancer drugs remains a challenge [14,15]. To ensure the earliest possible availability of therapeutic innovations while guaranteeing full reimbursement to patients, France has had the ATU system in place since 1994, allowing exceptional use, after in-depth

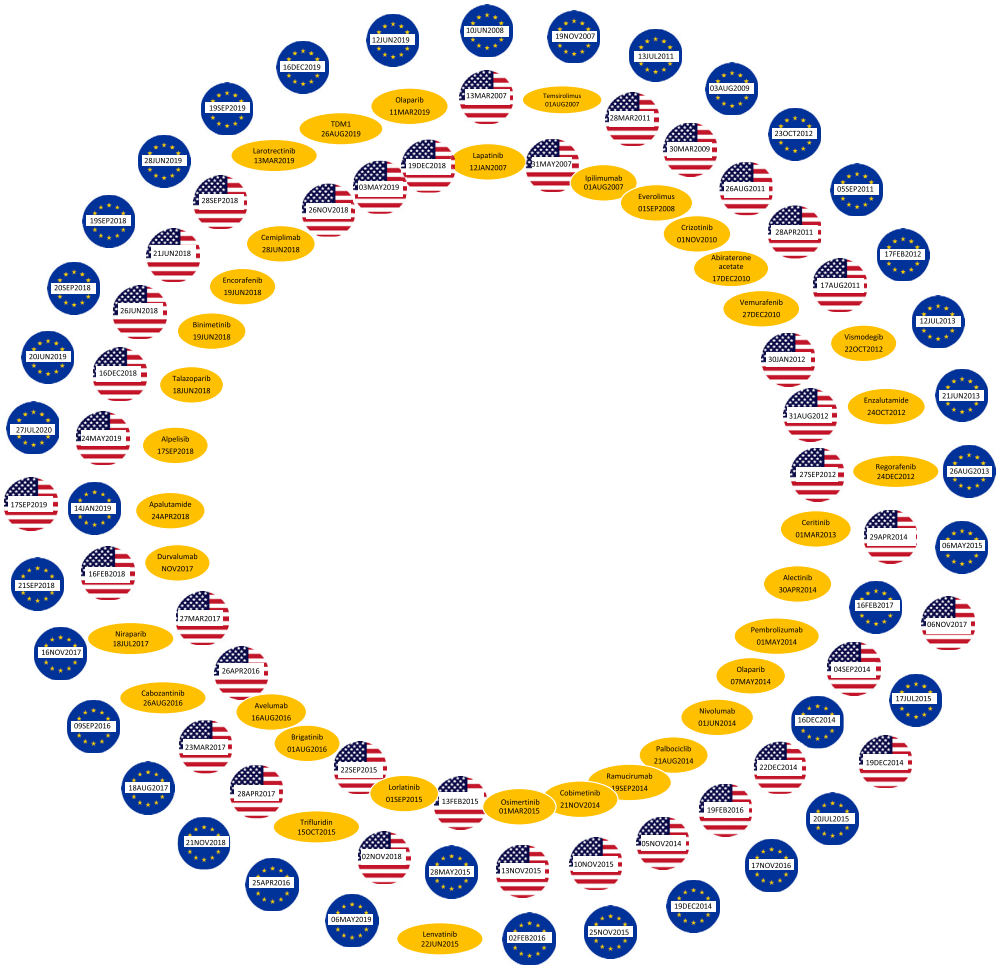

Fig. 4. Date of ATU initiation and EMA and FDA approval for each drug. In yellow: ATU start date; American flag: FDA approval; and European flag: EMA approval. EMA, European Medicines Agency; FDA, US Food and Drug Administration. For the particular case of Larotrectinib, the ATU was validated before EMA approval, but was initiated after EMA approval.

assessment, of innovative antineoplastic treatments before MA at no cost to the patient, as the drugs are fully paid for by the Social Security. In this article, our objective has been to describe the particularities of this drug availability system, which allows the administration of a new drug in oncology outside a clinical trial and before market access, and to outline its impact on antineoplastic treatments over the last 13 years. This involves the accessibility and availability of the drugs as well as systematic affordability due to the system's coverage assistance.

Between January 2007 and December 2019, after exclusion of medicines that had been withdrawn post-approval, suspended, or refused by the EMA or the ANSM, as well as generics and biosimilars, 67 drugs were retained, of which 36 were granted ATU, that is, 54% of the new oncology drugs first approved in the period for an MA. The absence of ATU for the remaining drugs is explained by the fact that ATUc are issued on the initiative of the pharmaceutical company and ATUn are issued on the initiative of the prescribing physician. Thus, the main reason for the absence of ATU for a given drug would be that there has been no request from either the physician or the pharmaceutical company. Thirty-six antineoplastic treatments were eligible for ATUs, allowing 16,927 French people to benefit from them. This can be considered as a small number when compared to cancer incidence in France (382,000 per year [2]), and maybe explained by the fact that innovation in oncology mainly concerns metastatic/advanced cancers, at a specific and well-established stage under precise immunohistochemical and/or molecular conditions, that clinical trials take priority over ATU, and that physicians are not sufficiently informed about the ATU system.

The RTU differs from the ATUextension (ATUex) by the fact that, in the case of ATUex, the industrial firm is ready to apply for MA for the indication in question, whereas in the case of RTU, the industrial firm is not in the process of applying for MA for the indication in question. For example, Crizotinib was approved for ATU from 2010 to 2013 for the treatment of adult patients with ALK-positive NSCLC. It subsequently received an MA for the treatment of patients with locally advanced or metastatic ALK or ROS1-positive NSCLC. It now benefits from an RTU, starting from 27th December 2019 and lasts for 3 years, for the treatment of adult patients with locally advanced or metastatic NSCLC with a mutation of exon 14 of C-Met, after at least one line of platinum doublet therapy with or without immunotherapy, following the results of the phase II ACSe Crizotinib and METROS trials. Indeed, there was no therapeutic alternative in this indication.

EU legislation lays down harmonised rules to ensure the quality, safety and efficacy of medicines. Medicinal products can only be marketed in the EU if they have been granted an MA by the EC or by the competent national authorities. Directive 89/105/EEC, adopted at the end of the 1980s, sets out the minimum procedural requirements to ensure the transparency of national pricing and reimbursement measures. These requirements include compliance with specific time limits for individual pricing and reimbursement decisions (90 d for pricing, 90 d for reimbursement or 180 d for combined decisions) [15]. The average approval time for drugs in the EU is 418 d [16]. In general, patients in the USA have access to newer, more effective drugs earlier, presumably because of the frequent use of expedited review procedures [17]. In Japan, the approval time has decreased from 1239 d in 1998 to 531 d in 2002 [18]. Although the reimbursement of antineoplastic drugs did not usually follow the 180-d recommendation, in accordance with the directive of the European Parliament and the Council, the ATU system made these drugs available to patients well before approval in other countries [15,19].

Nevertheless, other countries have developed early access programs, notably the USA. The FDA allows three types of early access: one for individual patients when they have a serious, life-threatening condition for which there is no other treatment option; one for a patient population when the investigational drug is not being actively developed; and finally, expanded access to a large population to bridge the gap between the completion of clinical trials and marketing approval [20]. Following accelerated approval, pharmaceutical companies are required to conduct post-approval clinical trials to confirm that the drug provides clinical benefit, as predicted by the surrogate end-point. From 1992 to 2010, the FDA granted accelerated approval to 35 oncology products for 47 new indications. However, clinical benefit was confirmed in post-approval trials for 26 of the 47 new indications, resulting in conversion to regular approval [21]. In addition, the federal 'Right to Try' act was signed into law on 30th May 2018 to create an additional way, different from the FDA's expanded access, for patients to gain access to an investigational, out-of-study drug, when the patient, the physician and the manufacturer all agree on its use. This is the case when a trial is not available, either because there is no room for recruitment, even when the trial itself is open, or because the patient cannot meet one or more of the trial's eligibility criteria. Eligible drugs are those that are not approved by the FDA for any indication, have completed a phase I trial, have an ongoing pivotal trial and have an active registration plan [22]. The EMA has also developed an early access program including PRIME (priority medicines) combining three different approaches: accelerated assessment, conditional MA and opinion for compassionate use [23]. Accelerated evaluation is the rapid assessment of drugs of major public health

interest, particularly therapeutic innovations. Next, conditional MA accelerates access to drugs that meet medical needs (fatal diseases, orphan drugs, emergencies). Finally, compassionate use refers to the use, under strictly controlled conditions, of an unauthorised drug in individual patients suffering from a fatal, long-term or severely debilitating disease for which there is no effective authorised treatment. Each Member State coordinates and implements its own compassionate use program, laying down specific rules and procedures. The medicinal product may still be in the clinical trial phase without a clear safety profile and dosage. Although early access programs appear to provide a real benefit in terms of public health, their development is limited by several issues, including the high risk of safety-related label changes.

Moreover, access to cancer drugs should be regarded through two perspectives: the first is market access through clinical trials or approval of the drugs; and the second is approval of the drugs to be reimbursed or covered by the medical system of each country. As an example, American access is usually described as a favourable system in terms of time to access, but approval of the drug through the FDA does not mean that the drug will be covered by specific insurance (Medicare, or other private insurance). Market access and coverage by Social Security or private insurance are clearly two evaluation methods that do not obey the same evaluation process. Market access is based on an evaluation of the risk/benefit ratio of a new medication, while the reimbursement process involves a comparison of several risk/benefit ratios from several therapeutics strategies to choose the best one. In France, coverage by Social Security is independent of the price of the drug and only depends on the comparison of the benefit/risk ratios between the different therapeutic alternatives (relative benefit/risk ratio). The cost-effectiveness ratio is analysed after the reimbursement decision [24]. According to a recent OECD report, products/indications are, on average, approved in OECD/EU countries 12–17 months after the first MA, which most often took place in the USA [19]. Patient access to antineoplastic drugs varies in Europe, resulting in varying lead times for MA and drug availability. Indeed, countries have different healthcare systems, both administratively and technically. The availability of the drug depends not only on the date of MA but also and above all on the date of reimbursement. Two countries are exceptions to this: England and Germany, where all authorised drugs are reimbursed by default. Nevertheless, in England, drug uptake can radically change according to the National Institute for Health and Care Excellence evaluation [19]. Another exception is France with its ATU system allowing early access to medicines before MA and reimbursement. But beyond the administrative aspects of each Health Insurance scheme, the difficulty of access to treatment is also due to other factors: the growing number of new therapies with various indications, uncertainty about the clinical benefit and the increasing price of new molecules. Finally, the financial coverage granted to medicines also differs, thus making the affordability of antineoplastic therapies highly diverse among patients [25–30]. A previous study by Varol *et al.* reported a launch time of approximately 2 years between 1995 and 2008 versus 4 years before 1995 [31]. The creation of the EMA and harmonisation of regulatory requirements in OECD countries explain the reduction in delays. This cooperation between regulatory authorities has increased in recent years to minimise these delays and improve access [25]. However, it does not guarantee that the new indication will be covered and be affordable for patients.

In conclusion, this article shows that the ATU system allows patients to benefit from therapeutic innovations before MA in different countries, including the USA, with full coverage. In many countries, the development of early access programs allows to effectively reduce drug access times. Improving access to care while assuring optimal drug safety still remains a challenge in oncology.

Data sharing

The data sets generated and/or analysed during the present study are not publicly available due to confidentiality but are available from the corresponding author on reasonable request.

Authors' contributions

Each author equally helped write the manuscript.

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Conflict of interest statement

The authors declare that they have no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2021.03.008.

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 Canc 2019;144(8):1941–53.

[2] Estimations nationales de l'incidence et de la mortalité par cancer en France métropolitaine entre 1990 et 2018. Institut National du Cancer; 2019.

[3] Arnold M, Rutherford MJ, Bardot A, et al. Progress in cancer survival, mortality, and incidence in seven high-income countries 1995-2014 (ICBP SURVMARK-2): a population-based study. Lancet Oncol 2019;20(11):1493–505.

[4] Hanna TP, King WD, Thibodeau S, et al. Mortality due to cancer treatment delay: systematic review and meta-analysis. BMJ 2020; 371:m4087.

[5] Martinalbo J, Bowen D, Camarero J, et al. Early market access of cancer drugs in the EU. Ann Oncol 2016;27(1):96–105.

[6] Proposition de loi visant à garantir à chacun un droit d'accès aux médicaments et dispositifs innovants. [in French]. https://www.assemblee-nationale.fr/dyn/15/textes/l15b2153_proposition-loi.pdf.

[7] Article L.601-2 (new article L.5121-12) created by the 21st article of the law no 92-1279 of December 8th, 1992, French public health code [in French] Journal Officiel de la République Française 1992:16888. no 288.

[8] Emmerich J, Dumarcet N, Lorence A. France's new framework for regulating off-label drug use. N Engl J Med 2012;367(14): 1279–81.

[9] Articles R5142-20 to R5142-30 created par the decree no 94-568 of July 8th, 1994, French public health code [in French] Journal Officiel de la République Française 1994;159:9981.

[10] ATU nominative – Liste des spécialités autorisées – ANSM: Agence nationale de sécurité du médicament et des produits de santé [in French]. https://www.ansm.sante.fr/Activites/Autorisations-temporaires-d-utilisation-ATU/ATU-nominative-Liste-des-specialites-autorisees/(offset)/5.

[11] ANSM. Avis aux demandeurs d'Autorisation temporaire d'utilisation (ATU) [in French]. ANSM; 2014. https://www.ansm.sante.fr/Activites/Autorisations-temporaires-d-utilisation-ATU/Faire-une-demande-d-autorisation-temporaire-d-utilisation/(offset)/5.

[12] ATU de cohorte en cours – ANSM : Agence nationale de sécurité du médicament et des produits de santé [in French]. https://www.ansm.sante.fr/Activites/Autorisations-temporaires-d-utilisation-ATU/ATU-de-cohorte-en-cours/(offset)/4.

[13] Comité économique des produits de santé. French Ministry of Health. [in French]. https://solidarites-sante.gouv.fr/ministere/acteurs/instances-rattachees/article/ceps-comite-economique-des-produits-de-sante.

[14] Albin N, Mc Leer A, Sakhri L. Precision medicine: a major step forward in specific situations, a myth in refractory cancers. Bull Canc 2018;105(4):375–96.

[15] European Parliament and Council of the European Union. Article 83 of the Regulation EC/726/2004 laying down community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency. Strasbourg: European Parliament; 31 Mar 2004. Off J Eur Union 2004. L 136/1-33.

[16] Hartmann M, Mayer-Nicolai C, Pfaff O. Approval probabilities and regulatory review patterns for anticancer drugs in the European Union. Crit Rev Oncol Hematol 2013 Aug;87(2):112–21.

[17] Roberts SA, Allen JD, Sigal EV. Despite criticism of the FDA review process, new cancer drugs reach patients sooner in the United States than in Europe. Health Aff 2011 Jul;30(7):1375–81.

[18] Ono S, Yoshioka C, Asaka O, et al. New drug approval times and clinical evidence in Japan. Contemp Clin Trials 2005;26(6): 660–72.

[19] OECD. Addressing challenges in access to oncology medicines. OECD Health Policy Studies. OECD Publishing. https://www.oecd.org/health/health-systems/Addressing-Challenges-in-Access-to-Oncology-Medicines-Analytical-Report.pdf.

[20] Jarow JP, Lurie P, Ikenberry SC, et al. Overview of FDA's expanded access program for investigational drugs. Ther Innov Regul Sci 2017;51(2):177–9.

[21] Johnson JR, Ning YM, Farrell A, et al. Accelerated approval of oncology products: the food and drug administration experience. J Natl Cancer Inst 2011;103(8):636–44.

[22] Shapiro RS. Reconciling states' "right to Try" legislation and FDA's expanded access program: legal issues. Ther Innov Regul Sci 2017;51(2):153–6.

[23] Support for early access. EMA. https://www.ema.europa.eu/en/human-regulatory/overview/support-early-access.

[24] Doctrine de la Commission de la Transparence. French National Authority on Health. [in French]. https://www.has-sante.fr/upload/docs/application/pdf/2018-10/doctrine_10102018.pdf.

[25] OECD. Pharmaceutical Innovation and Access to medicines, OECD health policy studies. OECD Publishing; 2018. http://www.oecd.org/health/health-systems/Pharmaceutical-Innovation-and-Access-to-Medicines-Executive-Summary-ENGLISH.pdf.

[26] Cole A, Towse A, Zamora B. Indication-Based pricing (IBP) discussion paper. London: Office of Health Economics; 2019. https://www.ohe.org/publications/indication-based-pricing-ibp-discussion-paper-should-drug-prices-differ-indication#.

[27] Cherny N, Sullivan R, Torode J, et al. ESMO European Consortium Study on the availability, out-of-pocket costs and accessibility of antineoplastic medicines in Europe. Ann Oncol 2016;27: 1423–43.

[28] Aggarwal A, Ginsburg O, Fojo T. Cancer economics, policies and politics: what in forms the debate? Lessons from the EU, Canada and US. J Canc Pol 2014;2:1–11.

[29] Netzer T. European Union centralised procedure for marketing authorisation of oncology drugs: an in-depth review of its efficiency. Eur J Canc 2006;42:446–55.

[30] Hofmarcher T, et al. Comparator report on cancer in Europe 2019 – disease burden, costs and access to medicines. Lund, Sweden: IHE; 2019.

[31] Varol N, Costa-Font J, McGuire A. Do international launch strategies of pharmaceutical corporations respond to changes in the regulatory environment? The LSE Companion to Health Policy 2012. https://doi.org/10.4337/9781781004241.00022.