ACCESS TO ONCOLOGY DRUGS: INSIGHTS FROM FRANCE'S EARLY ACCESS REFORM

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BACKGROUND

In July 2021, France significantly reformed the Early Access (EA) process**,** replacing the former **Authorization for Use (ATU) system**. This reform aimed to simplify procedures and accelerate access to innovative drugs**. Two pathways of EA, compassionate access (ACU) and authorizations for early access (AEA)** were implemented instead of 6 in the former ATU system.

AEA concerns drugs in specific indications, aiming at treating serious, rare, or debilitating diseases. AEA is applicable both before marketing authorization (MA) by EMA or in "Post-MA" (when the drug is approved by EMA but not yet reimbursed/priced). Conversely, ACU allows the use of drugs without MA indications in France, not intended for registration.

The reform also changes the procedure pathway: whereas ATU was only regulated by the French Medicines Agency (ANSM, Agence nationale de sécurité du médicament et des produits de santé), **the National Health Authority (HAS, Haute Autorité de Santé) is now also involved in AEA decisions**. ANSM and HAS are expected to deliver a common decision within **90 days to allow patients prompt access to drugs**.

A first study providing a two-year assessment of the EA reform in France (1) shows that most of AEA were granted for oncology drugs (52% of the indications), and applications were mostly supported by high-level evidence studies (phase III trials) with mature overall survival data provided. The number of oncology patients treated significantly increased compared to the previous ATU period (+484%, with 18,341 patients in 2022).

The present study aimed **to evaluate the impact of EA reform at three years, in terms of drug granted and their characteristics, number of treated patients, treatment lines and indications.**

OBJECTIVE

By focusing on oncology (including onco-hematology) drugs, this study aims to review the first 30 months of the reform :

- To examine the characteristics of drug approvals through the AEA process and assess the methodological quality of clinical trials supporting these requests,
- To quantify the impact of the reform in real-life conditions, regarding the number of patients treated, by tumor site and by treatment line.

PATIENTS AND METHODS

The study focuses only on AEA to concentrate on drugs who are intended to be marketed and followed a two-step methodology:

1. Number and Characteristics of Drugs Approved:
All oncology applications submitted to the HAS since the EA reform (from July 1, 2021) until December 31, 2023 were identified, reviewing approval decisions, timelines, and reasons for acceptance or rejection. The therapeutic class (ATC), cancer site and stage were identified in the HAS website. The methodological characteristics and evidence of trials supporting EA decision (approvals/rejections) was done using data extracted from clinicaltrial.gov, except for renewals, treatment combination and antidote.

2. Real-World data on the number and the characteristics of patients treated by an EA drugs: an observational retrospective longitudinal study was conducted using the French Nationwide Claims Database (SNDS) for the period between January 1, 2019, and December 31, 2023. The SNDS database covered more than 99% of the French population and includes claims data from both hospital and community care across public and private sectors (2). For each EA approved drug, we identified the number of patients treated monthly, by tumor localization and treatment line.

RESULTS

1 Characteristics of drug demands trough the EA pathway

By December 31, 2023, 249 demands for AEA have been submitted to the HAS.
Among the 213 decisions published, **106 (50%) concerned oncology indications.**
The **acceptance rate for oncology indications is 83%** (88 accepted and 18 denied).
Regarding the HAS criteria, refusals were mainly justified by the presence of competitors (63% of refusals), the possibility to differ the treatment (70% of refusals) of the fact that the treatment was not considered as innovative (70% of refusals).

Regarding the delay in decisions, **HAS and ANSM have rendered EA decisions within 71 days on average** [range: 13- 190], and in less than 90 days in 87% of cases.

Excluding renewals and drugs associations, 48 drugs for 53 indications in oncology received EA approval, predominantly monoclonal antibodies or **antibody drug conjugates** (26, 49%), CAR-T cell therapies (9, 17%) and other neoplastic agents (8, 15%).

Most approved indications were in solid oncology (35, 66%), mainly in digestive (23%), urological (23%), or breast cancers (20%), in metastatic indications in the first line (11, 21%) or second line (8,15%). Onco-hematology authorizations accounted for 18 indications (34%), mostly in the third line and beyond (10, 19%).

As shown in Table 1, oncology drugs approved were primarily backed by **phase III trials (70%), including direct comparison (66%) and/or randomization (70%)** whereas refused EA drugs were frequently supported by indirect comparison or non-comparative trials (50%). **Overall survival (OS) was included as primary or secondary endpoints in 23% and 62%** of approved EAs, with **mature data available in 36% of trials.**

Table 1 : Characteristics of oncology EA decisions

	Early access decision granted (n=53)	Early access decision denied (n=16)
Characteristics of the drugs - Therapeutic class (n, %)		
Radiopharmaceuticals	3 (6%)	0 (0%)
Antineoplastic agents		
Alkylating agents	1 (2%)	0 (0%)
Antimetabolites	1 (2%)	0 (0%)
Antineoplastic cell and gene therapy – (CAR T cells therapy)	9 (17%)	0 (0%)
Monoclonal antibodies and antibody drug conjugates	26 (49%)	3 (19%)
Other antineoplastic agents	8 (15%)	5 (31%)
Protein kinase inhibitors	5 (9%)	8 (50%)
Cancer situation and therapy line of the claimed indication (n, %)		
Solid tumors		
Localized situation, adjuvant	7 (13%)	3 (19%)
Localized situation, neo adjuvant	2 (4%)	0 (0%)
Metastatic situation, diagnostic	2 (4%)	0 (0%)
Metastatic situation, 1st line	11 (21%)	4 (25%)
Metastatic situation, 2nd line	8 (15%)	2 (%)
Metastatic situation, ≥ 3 lines	5 (9%)	1 (%)
Hematological malignancies		
1st line	2 (4%)	1 (0%)
2nd line	6 (11%)	4 (%)
≥ 3 lines	10 (19%)	1 (0%)
Characteristics of clinical trials (n, %)		
Development phase		
I, I/II	9 (17%)	4 (25%)
II	7 (13%)	3 (19%)
III	37 (70%)	9 (56%)
Study type		
Comparative study	38 (72%)	9 (56%)
Direct comparison	35 (66%)	8 (50%)
Indirect comparison	2 (4%)	0 (0%)
Basket trial	1 (2%)	0 (0%)
Non comparative study	15 (28%)	7 (44%)
Randomized study	37 (70%)	8 (50%)
Double blind study	37 (70%)	2 (13%)
Primary Endpoint		
Overall survival (OS)	12* (23%)	1 (6%)
Overall response rate (ORR)	13*(25%)	9 (56%)
Progression free survival (PFS)	21* (40%)	5 (31%)
Other	8*(15%)	1 (6%)
Exploration of OS		
OS as primary endpoint or co-primary endpoint	12 (23%)	1 (6%)
OS as secondary endpoint	33 (62%)	12 (75%)
Indirect comparison	0 (0%)	1 (6%)
Non included	3 (6%)	2 (13%)
Maturity of OS data		
Mature OS data	19 (36%)	2 (13%)
Non mature OS data	25 (47%)	9 (56%)
NA	9 (17%)	5 (31%)

2 Real-word data on patients receiving an EA drug

Figure 1: Evolution on the number of patients treated by an EA drug, by tumor type

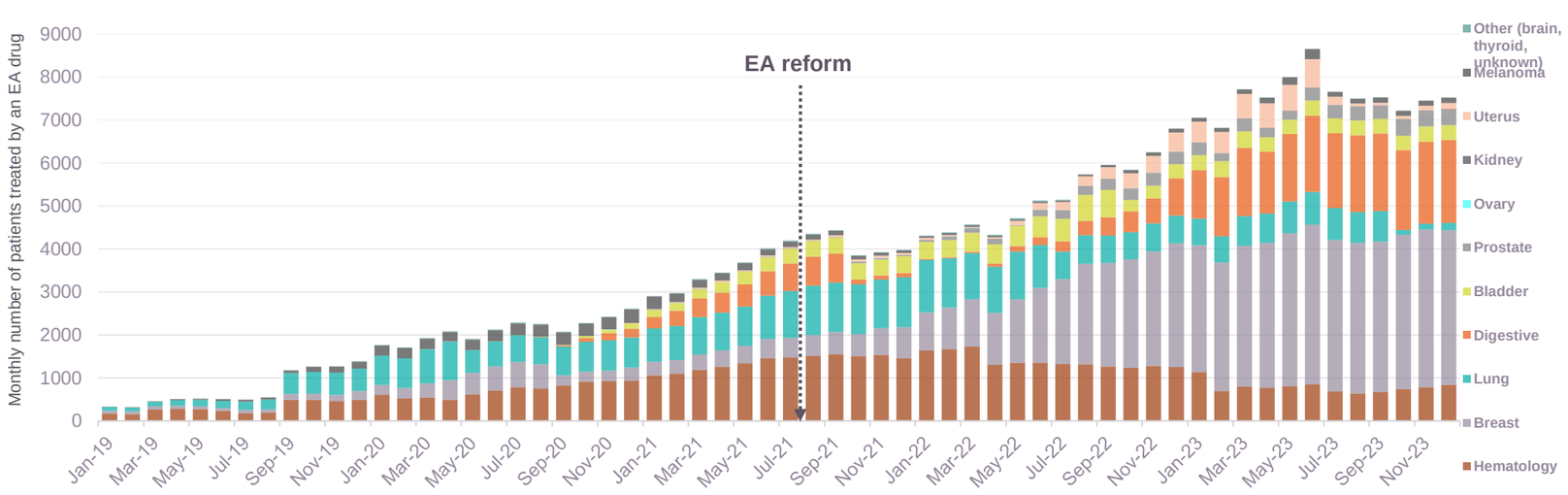
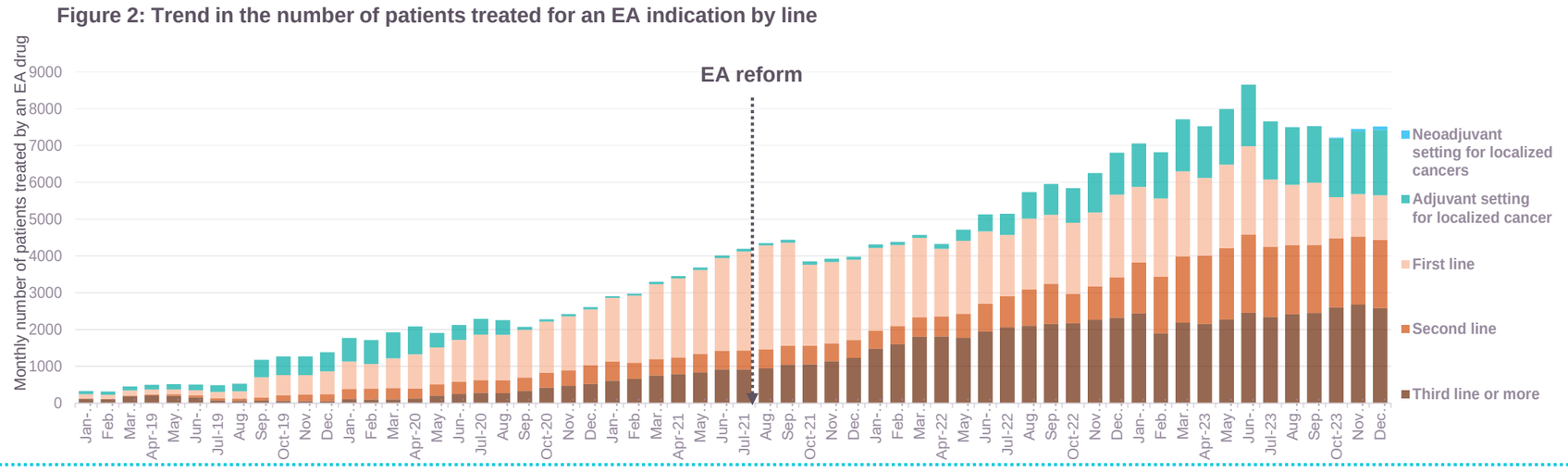


Figure 2: Trend in the number of patients treated for an EA indication by line



The number of patients treated monthly with an oncology AEA treatment has risen steadily, being multiplied by 22 over the period, from 330 in Jan 2019 to 7,521 in Dec 2023. Patients are mainly treated for **breast** (from 68 to 3,595 patients, +5187%) or **digestive cancers** (from 0 to 1927 patients). New localizations have also emerged like **bladder and prostate cancers,** with 342 and 363 patients in December 2023, respectively. Other indications are slowly decreasing like lungs cancer (174 patients treated in Dec 2023 vs 1221 in Jan 2022). **Hemato-oncology,** which represented approximately half of the treated patients in January 2019 (168 patients), saw an increase in its number of patients (839 patients in Dec 2023) and **represents now only 11% of patients treated in Dec 2023. (Figure 1)**
Since the EA reform, whereas EA indications mostly concerned 1st line patients before the reform, patients in 1st, 2nd or 3rd line and in adjuvant and neoadjuvant settings are now treated with EA drugs. (Figure 2)

CONCLUSION

The French EA reform has facilitated rapid access to innovative therapies with strong evidence, while simplifying the previous regulatory frameworks. Over half of the approvals have been for oncology indications, primarily targeting solid tumors, with monoclonal antibodies and antibody-drug conjugates.
The AEA process is significantly faster than both the current drug reimbursement process and the previous ATU system, which required 503 days (3) and 257 days (4), respectively. Additionally, the approved indications were backed by high-quality methodological trials, with ~70% involving comparative phase III trials featuring direct comparisons, and overall survival (OS) as primary endpoint. This underscores the continued importance of OS outcomes as a key criterion in the French regulatory context, contrasting with the FDA's cancer accelerated approvals, which often rely on overall response rates (ORR) from early-phase or single-arm trials (5).
A substantial increase in the number of patients receiving AEA treatments between 2019 and 2023 was observed, with 7,521 patients treated in December 2023, corroborating the findings our previous study on the impact of the French EA reform (1). This rising number of treated patients may be explained by the concurrent availability of new drugs under EA and the expansion of indications for existing drugs across multiple therapeutic areas, a trend also observed in other countries (6,7).

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References : (1) Martin T, Rioufol C, Favier B, Martelli N, Madelaine I, Chouaid C, Borget I. Impact of Early Access Reform on Oncology Innovation in France: Approvals, Patients, and Costs. BioDrugs. 2024 May;38(3):465-475. doi: 10.1007/s40259-024-00658-1. Epub 2024 Apr 20. PMID: 38643301. (2) Scailteux L-M, Droitcourt C, Balusson F, Nowak E, Kerbrat S, Dupuy A, et al. French administrative health care database (SNDS): The value of its enrichment. Therapies. 2019;74:215–23. (3) Newton M, Stoddart K, Travaglio M, Troein P. EFPIA Patients W.A.I.T. Indicator 2023 Survey. (4) LEEM. Bilan économique 2021 des entreprises du médicament - Edition 2022 [Internet]. [cited 2023 Aug 4]. Available from: https://www.leem.org/publication/bilan-economique-2021-des-entreprises-du-medicament-edition-2022 (5) Agrawal S, Arora S, Amiri-Kordestani L, de Claro RA, Fashoyin-Aje L, Gormley N, et al. Use of Single-Arm Trials for US Food and Drug Administration Drug Approval in Oncology, 2002-2021. JAMA Oncology [Internet]. 2022 [cited 2023 Jan 11]; Available from: https://doi.org/10.1001/jamaoncol.2022.5985 (6) Jacquet E, Kerouani-Lafaye G, Grude F, Goncalves S, Lorence A, Turcry F, et al. Comparative study on anticancer drug access times between FDA, EMA and the French temporary authorisation for use program over 13 years. European Journal of Cancer. 2021;149:82–90. (7) Trends in the approval of cancer therapies by the FDA in the twenty-first century | Nature Reviews Drug Discovery [Internet]. [cited 2023 Jul 27]. Available from: https://www.nature.com/articles/s41573-023-00723-4