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## Impact of Early Access Reform on Oncology Innovation in France: Approvals, Patients, and Costs

Tess Martin, Catherine Rioufol, Bertrand Favier, Nicolas Martelli, Isabelle  
Madelaine, Christos Chouaid, Isabelle Borget

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1 **Impact of Early Access Reform on Oncology Innovation in France: Approvals, Patients, and**  
2 **Costs**

3 Tess Martin<sup>1,2</sup>, Catherine Rioufol<sup>3,4</sup>, Bertrand Favier<sup>5</sup>, Nicolas Martelli<sup>1,2</sup>, Isabelle Madelaine<sup>6</sup>,  
4  
5 Christos Chouaid<sup>7,8</sup>, Isabelle Borget<sup>9,10</sup>

7 Affiliations:

10 <sup>1</sup>Pharmacy Department, Georges Pompidou European Hospital, AP-HP, 20 Rue Leblanc, 75015, Paris,  
11 France.

14 <sup>2</sup>Paris-Saclay University, GRADES, Faculty of Pharmacy, 17 Av. des Sciences, 91400 Orsay, France.

17 <sup>3</sup>Pharmacy Department, Lyon Sud Hospital, Hospices Civils de Lyon, Lyon, France.

19 <sup>4</sup>EA3738, CICLY, UCBL1, Lyon, France

21 <sup>5</sup>Centre Léon Bérard, Pharmacy Department, 28 rue Laennec, 69008 Lyon, France

23 <sup>6</sup>Pharmacy Department, Saint-Louis Hospital, AP-HP, 1 avenue Vellefaux 75010 Paris, France, Vice  
24 president of Société Française de Pharmacie Oncologique (SFPO)

27 <sup>7</sup>Service de Pneumologie, CHI Créteil,

29 <sup>8</sup>Inserm U955, UPEC, IMRB, Créteil France

32 <sup>9</sup>Gustave Roussy, Biostatistics and Epidemiology Office, Université Paris-Saclay, Villejuif, France

34 <sup>10</sup>Inserm, Université Paris-Saclay, CESP U1018, Oncostat, labeled Ligue Contre le Cancer, Villejuif,  
35 France

38 **Corresponding author:** Tess Martin

41 Paris-Saclay University, GRADES, Faculty of Pharmacy, 17 Av. des Sciences, 91400 Orsay, France.

43 Tel: +33156092575

46 E-mail: [tess.martin@universite-paris-saclay.fr](mailto:tess.martin@universite-paris-saclay.fr)

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## Abstract

32

### 33 Background

34 An ambitious reform of the Early Access (EA) process was set up in July 2021 in France, aiming to simplify  
35 procedures and accelerate access of innovative drugs.

### 36 Objective

37 This study analyzes the characteristics of oncology drug approvals through the EA process, and its impact in real-  
38 life data for oncology patients.

### 39 Methods

40 The number and characteristics of EA demands concerning oncology drugs submitted to the National Health  
41 Authority (HAS) were reviewed until December 31, 2022. A longitudinal retrospective study on patients treated  
42 with an EA oncology drug between January 1, 2019, and December 31, 2022 was also performed using the French  
43 Nationwide claims database (SNDS) to assess the impact of the reform in number of indications, patients and  
44 costs.

### 45 Results

46 Among 110 published decisions, HAS granted 88 (80%) EA indications within 70 days of assessment on average,  
47 including 46 (52%) in oncology (67% in solid tumors and 33% in hematological malignancies). Approved  
48 indications were mostly supported by randomized phase III trials (67%), whereas refused EA relied more on non-  
49 randomised (57%) trials. Overall survival was the primary endpoint of 28% of EA approvals *versus* none of denied  
50 EA. In the SNDS data, the annual number of patients with cancer treated with an EA drug increased from 3,137  
51 patients in 2019 to 18,341 in 2022 (+484%), whereas the number of indications rose from 12 to 62, mainly in  
52 oncohematology (n=17), lung (n=12), digestive (n=9) and breast cancer (n=9). Reimbursement costs for EA  
53 treatments surged from €42 to €526 million (+1159%).

### 54 Conclusion

55 The French EA reform contributed to enabling rapid access to innovations in a wide range of indications for  
56 oncology patients. However, the findings highlight ongoing challenges in financial sustainability, warranting  
57 continued evaluation and adjustments.

58

### 59 Key points:

- 60 • The early access reform in France has enabled rapid access to innovation, particularly for oncology drugs.

61 • Approved oncology drugs are mostly supported by high-level evidence studies (phase III trials) with  
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2 62 mature overall survival data provided.

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4 63 • The reform also led to a significant increase in the annual number of patients treated and reimbursement  
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6 64 costs.

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## MAIN TEXT

66

### 1.INTRODUCTION

67 Cancer is a major public health concern. In 2020, there were 2.7 million new cases in the European Union (EU)  
68 countries, leading to 1.3 million deaths[1]. Cancer-related deaths are expected to rise by over 24% by 2035, making  
69 it the leading cause of death[2], even with therapeutic innovations.

70  
71 Drugs innovations, as targeted therapies, immunotherapies or CAR-T cells, have represented a significant  
72 breakthrough in the treatment of advanced cancer, significantly improving overall survival and patient's quality  
73 of life[3,4]. However, the process of reimbursement and drug pricing has become much more complex and  
74 prolonged, taking 503 days on average after the EMA approval in France [5]. Since then, access to medicines in  
75 the EU has been accelerated, largely encouraged by the 'Europe's beating cancer' plan[6], and various schemes  
76 have emerged[7], such as the PRIME (priority medicines) programme for medicines to address unmet needs[8].

77 Early access programs (EAPs) are designed to provide patients access to medicines before their marketing  
78 authorization (MA) or during the national reimbursement & pricing process. In 1994, France was pioneer by  
79 implementing an EAP framework called authorization for temporary use (ATU)[9]. Due to successive  
80 modifications over time, the ATU system became however increasingly complex with six different pathways[10].  
81 Concomitantly, expenditures related to innovative drugs (including those in ATU program) continued to rise  
82 significantly in France, exhibiting an annual growth rate of 54% between 2019 and 2022. Among these, oncology  
83 drugs have seen their costs more than triple over the past three years[11].

84 In July 2021, an ambitious reform of the French early access (EA) system was thus implemented with three main  
85 objectives : to simplify and harmonize procedures for EA to innovative drugs, allow patients faster access to drugs,  
86 and guarantee financial sustainability for the healthcare system[12]. Two pathways now exist: authorization for  
87 early access (AEA) and authorization for compassionate use (ACU). AEA concerns drugs in specific indications,  
88 aiming at treating serious, rare or debilitating disease, when all the following criteria are met: (i) in exceptional  
89 circumstances, (ii) no appropriate treatment exists, (iii) treatment cannot be postponed, (iv) efficacy and safety of  
90 the drug are highly presumed according to clinical trials and (v) the drug is presumed innovative in regards to a  
91 possible clinically meaningful comparator. AEA is applicable both to drugs in "Pre-MA" EA (before MA by EMA)  
92 or in "Post-MA" EA (MA is approved by EMA that not yet reimbursed/priced)[13]. Conversely, ACU allows, the  
93 use of drugs without MA indications in France to treat severe or rare diseases when there is no appropriate  
94 treatment available, the patient cannot be enrolled in a clinical trial, and the implementation of treatment cannot  
95 be delayed. This applies to drugs not intended for registration or marketing. For example, EA has been granted for

96 therapeutic innovations such as CAR T cell therapy and antibody drug conjugates for severe solid tumors and  
1 97 hematologic malignancies. Additionally, compassionate use has been granted for certain drugs already on the  
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3 98 market but lacking marketing authorization for specific indications, such as dapsone for the treatment of  
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5 99 autoimmune bullous dermatosis.  
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8 100 The reform also changes the procedure pathway: whereas ATU was only regulated by the French Medicines  
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10 101 Agency (ANSM, Agence nationale de sécurité du médicament et des produits de santé), the National Health  
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12 102 Authority (HAS, Haute Autorité de Santé) is now also involved in AEA decisions. ANSM and HAS are expected  
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14 103 to deliver a common decision within 90 days to allow patients prompt access to drugs. Regarding financing for  
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16 104 EA pathway, the drug is provided to hospitals at a price freely fixed by the manufacturer and communicated to the  
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18 105 Economic Committee for Healthcare Products (CEPS). However, two types of rebates are applied afterwards:  
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20 106 annual rebates based on the net invoiced turnover to hospitals, following a progressive scale set by decree. These  
21  
22 107 rebates can be increased if the manufacturer fails to adhere to the terms of the early access agreement. Additionally,  
23  
24 108 there are "unwinding" rebates based on the final negotiated price with the CEPS.  
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26 109 At the European level, various models of early access to medicines have also emerged. Spain regulates EAPs under  
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28 110 Royal Decree 1015/2009, mainly nominal-based but with some cohort-based options like compassionate use. The  
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30 111 UK's Early Access to Medicines Scheme (EAMS) covers pre-MA drugs for all trial-eligible patients, offered as  
31  
32 112 either nominal or cohort-based. In Italy, multiple lists oversee early access and off-label use, including Law 648/96,  
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34 113 Well-Established Use, and the 5% Fund. While Italy has shown generosity in implementing EAPs, it faces  
35  
36 114 challenges due to mixed approaches combining early access with off-label use. The comparative study of these  
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38 115 different early access systems has led researchers to consider the French EA reform as a potential model for  
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40 116 harmonizing different European EAP.[7,13,14]. However, there is currently insufficient data assessing the impact  
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42 117 in terms of drug approvals and number of treated patients in France, and no economic data is available since the  
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44 118 EA reform[7,15,16]. This study aims to review the first 18 months of the reform, focusing on oncology (including  
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46 119 hematological malignancies) drugs following an AEA decision. The objectives were to analyse the characteristics  
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48 120 of oncology drug approvals through the new AEA process and to evaluate the impact of the reform in real-life, in  
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50 121 terms of number of indications, number of treated patients and costs, using the nationwide claims database.  
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54 123 **2.MATERIAL AND METHODS**  
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56 124 The present study follows a two-step approach. First, it used the National Health Authority data to identify and  
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58 125 analyse the characteristics (number, acceptance rate, delay for decision, tumor type, methodological issues of the  
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126 trial) of the AEA demands related to oncology drugs since the reform (July 1, 2021). Secondly, a longitudinal  
1 127 study using data from the French Nationwide claims reimbursement database (SNDS) from 2019 to 2022 was  
2 128 performed to evaluate the impact of the AEA reform in real-life conditions, in terms of number of drugs/indications  
3 129 used, number of patients treated and reimbursement costs.  
4 130

### 2.1 Number and characteristics of drug demands to the AEA pathway

10 131 All the AEA demands submitted to the HAS since the reform (July 1, 2021) until December 31, 2022 were  
11 132 identified and reviewed. Given that HAS is now responsible for AEA decisions, all the information's regarding  
12 133 the corresponding demands are now available on the HAS website[17]. It included information regarding the drug,  
13 134 the claimed indication, the eligibility criteria to AEA program, the pivotal data supporting the demand, the decision  
14 135 (approval/failure) and its reasons, and the submission and decision dates. Note that these dossiers are presented by  
15 136 indication (rather than by drug), as authorization and reimbursement occur on a per-indication basis.  
16 137

18 137 For oncology (solid tumors and hematological malignancies) indications, we collected the drug's name,  
19 138 therapeutic class (using WHO Anatomical Therapeutic Chemical classification[18]), the decision, and the time  
20 139 between submission and decision. Data related to the methodology of the main trial supporting the EA demand  
21 140 (phase, design, comparator, primary endpoint, presence of overall survival (OS) data and OS maturity if provided)  
22 141 were also collected and compared between approval and failure decisions. Combination therapies that submitted  
23 142 two similar demands were counted as a single one (n=4). Three demands for indication renewals with no significant  
24 143 modification were excluded, as well as one demand concerning an antidote (glucarpidase), considering it has no  
25 144 anti-tumor effect. Figure 1 presents the flowchart of the selected demands.  
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### 2.2 Real-word data on patients receiving an EA drug

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39 146  
40 146 The second part of our analysis aimed to quantify the impact of the AEA reform in real life conditions, regarding  
41 147 the number of drugs (or indications) administered, the number of patients treated by an EAE drug and their costs  
42 148 in France. To do that, we performed an observational retrospective longitudinal study using the nationwide claims  
43 149 database (SNDS) between January 1, 2019, and December 31, 2022. The SNDS database contains claims data for  
44 150 more than 99% of the French population, covering both hospital and community care and both the public and  
45 151 private sectors[19]. The SNDS uses a unique and anonymous patient identifier, so that individual patients can be  
46 152 followed over their lifetime. Regarding medicines, ATU/AE treatments administered or delivered at hospital are  
47 153 documented into the MEDATU/MEDAPAC database, including information on the drug code (UCD, *unite*  
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155 *commune de dispensation*), the indication code<sup>1</sup>, the anonymous patient identifier, the month and year of delivery  
156 and the reimbursement cost from the French National Health Insurance's perspective (in €), before discounts are  
157 applied. For each indication code identified, the molecule's name, reimbursement dates under ATU/EA pathway,  
158 therapeutic area and anatomical location can be retrieved using a Ministry of Health file[10].

159 All ATU/EA drug deliveries between 1 January 2019 and 31 December 2022 corresponding to solid tumours and  
160 haematological malignancies indications were extracted from the MEDATU/MEDAPAC databases. Analysis was  
161 restricted to indications included in the AEA pathway (from 07/01/2021 to 12/31/2022) and certain ATU  
162 indications (cohort ATU, "post-ATU," indication extension ATU, and direct access post-MAA, which later  
163 merged to become AEA status, during the period from 01/01/2019 to 06/30/2021), excluding ACU indications.  
164 For the selected indications, the number of indications used, the number of (prevalent) patients treated and the  
165 costs were calculated monthly and annually, and presented both globally and by tumor localisation.

166 Of note, the sum of the number of patients treated monthly is not equal to the number of patients treated annually,  
167 since patients are generally treated over several months.

168 Statistics were descriptive. Data from the HAS website were collected in Excel<sup>®</sup> (Microsoft Office 2016), whereas  
169 analyses from the SNDS data were conducted using SAS<sup>®</sup> software version 9.4.

170

## 171 **3.RESULTS**

### 172 **3.1Characteristics of drugs and demands approved under the AEA reform**

173 By December 31, 2022, 130 demands for AEA have been submitted by manufacturers to the HAS. Among the  
174 110 decisions published, 54 (49%) concerned oncology indications (67% in solid tumors and 33% in hematological  
175 malignancies). Across all therapeutic areas, the HAS has granted 88 (80%) positive access decisions, while the  
176 acceptance rate for oncology/hematological malignancies indications is 85%. Oncology drugs that were approved  
177 and their indication are listed in Supplementary Table 1. Another point is the speed in decisions, as HAS and  
178 ANSM have rendered them within 70 days on average [range: 47- 113], and in less than 90 days in 87% of cases.  
179 Regarding therapeutic classes, 21 (46%) approvals concerned monoclonal antibodies and antibody-drug  
180 conjugates drugs, 7 (15%) concerned protein kinase inhibitors (16%) and 6 (13%) concerned CAR-T cells agents.  
181 The methodological characteristics of the trials supporting the EA decisions are presented on Table 1, according  
182 if AEA was granted (n=39) or denied (n=7). Granted AEA were mostly supported by phase III trials (67%) that

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<sup>1</sup> A code provided by the French ministry used to label the drug under ATU/EA pathway in an authorized indication.

183 included a randomisation (69%), whereas refused AEA were mainly phase I or II trials (58%), mostly non-  
184 comparative (43%). The notion of comparator is important, as 51% of granted AEA had a clinically relevant  
185 comparator<sup>2</sup>. But trials *versus* placebo or supportive care were also accepted in 18% of cases, in accordance with  
186 the HAS methodological guide[21] that accepts them when justified, particularly for rare diseases or when no  
187 treatment exists. Regarding primary (or co-primary) endpoint, they were distributed among overall survival (OS,  
188 28%), progression free survival (PFS, 28%), overall response rate (ORR, 28%) or another endpoint (23%) for  
189 granted demands. OS was also explored as secondary endpoint in 25 (64%) of granted cases. Conversely, primary  
190 endpoints were mostly ORR (71%) or other endpoints (29%) but never OS or PFS for denied demands. To date,  
191 all demands having mature OS data (41% of cases) in a comparative trial were accepted, meaning that OS data  
192 remain a major endpoint, including for the EA process. For the 7 denied demands, the HAS considered that an  
193 appropriate treatment already existed in the indication (6/7), or/and that the drug was not presumed innovative  
194 (5/7).

### 3.2 Evolution of the number of indications, patients and cost for AEA oncology drugs

196 The figure 2 presents the evolution of the number of distinct ATU/EA indications of oncology drugs used in real-  
197 world practice from 2019 to 2022, by trimester. It showed that the number of indications strongly increased over  
198 the period, ranging from 12 ATU indications (7 for solid cancers and 5 for hematological malignancies) in 2019  
199 to 62 EA indications in 2022, predominantly in hematological malignancies (n=17), lung cancer (n=12), digestive  
200 cancer (n=9) and breast cancer (n=9). This may be explained by multiple extension of indications (like CAR-T  
201 cells in multiple myeloma or pembrolizumab in 4 indications (2 in breast, 1 in pancreatic and 1 in cervical cancers),  
202 the arrival of new therapeutic classes (2 indications for the trastuzumab deruxtecan in breast cancer and in digestive  
203 cancer or teclistamab), or the pursuit of treatment under EA reform.

204 As a possible consequence, the annual number of patients with cancer who were treated with an AEA drug strongly  
205 increased from 3,137 patients in 2019 to 18,341 in 2022 (+484%). The figure 3 shows the evolution of the number  
206 of patients treated by an AEA drug in France, by month and by tumor localization. It reveals that the number of  
207 patients treated monthly with an oncology AEA treatment has risen steadily, being multiplied by 20 over the

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<sup>2</sup> According to the definition of HAS transparency committee's doctrine, a clinically relevant comparator may be a medicinal product (active substance or placebo, with or without MA), a medical device, a procedure or any other non-medicinal therapy (or diagnostic method). It plays the same role in the therapeutic strategy as the new medicinal product and is aimed at the same patients.[20]

208 period, from 326 in Jan 2019 to 6,800 in Dec 2022. It mainly concerned patients treated for breast (from 68 to  
1 209 2,877 patients, +4131%) or lung cancers (from 84 to 650 patients, +674%). New localizations have also emerged  
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4 210 like digestive and urological cancers, with 866 and 619 patients in December 2022, respectively. Hemato-  
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6 211 oncology, which represented approximately half of the treated patients in January 2019 (168 patients), saw a  
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8 212 sevenfold increase in its number of patients (1251 patients in December 2022) and represents only 18% of patients  
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10 213 treated with an EA oncologic drug at the end of the study period.  
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12 214 Reimbursement costs also increase significantly, from 42 to 526 million (M) between 2019 and 2022 (+1159%).  
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14 215 In 2022, the higher reimbursement costs concerned treatments for hematological malignancies (180 M€), breast  
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16 216 cancer (159 M€), urology (68 M€), and lung cancer (64 M€). Figure 4 shows the evolution of monthly  
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18 217 reimbursement costs for AEA drugs in France by tumor localization.  
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#### 22 219 4.DISCUSSION

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24 220 With 88 indications approved within 18 months, the French early access reform has allowed rapid access to  
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26 221 innovations with a high level of evidence and a regulatory simplification of the previous EA systems. More than  
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28 222 half of approvals concerned oncology indications, predominantly for solid tumors, notably targeted kinase-  
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30 223 inhibitors and immunotherapy. The same trend is found in the US where roughly one-quarter of accelerated-  
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32 224 approved drugs are precision medicines for treating solid tumors since 1992[22]. This trend highlights the fact that  
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34 225 specific classes of innovative products dominate the oncology treatment landscape, testifying to the accelerated  
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36 226 pace of innovation in this field[23]. With decisions delivered within 70 days on average, ANSM and HAS comply  
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38 227 with the regulatory deadline in 87% of cases. This is outstanding as it granted immediate access for AEA drugs to  
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40 228 patients. The AEA process is notably quicker than the current drug reimbursement process and the previous ATU  
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42 229 evaluation, which required 503 days[5] and 257 days[24], respectively. In addition, approved indications were  
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44 230 supported by high-quality methodological studies, with mostly phase III trials including direct comparison,  
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46 231 randomisation and OS as primary endpoint in nearly one-third of cases, underlining the continued significance of  
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48 232 OS results as pivotal requirement in the French context. This differs from FDA approach for cancer accelerated  
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50 233 approvals, whom often rely on ORR data from early trial or single-arm trial[25]. It is however in accordance with  
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52 234 the French evaluation performed by the HAS for common drug reimbursement, which enhance drugs with  
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54 235 substantial clinical benefits supported by methodologically rigorous studies[13]. Previous studies also  
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56 236 demonstrated that ATU programs were based on robust approvals characterized by substantial enhancements in  
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58 237 clinical benefit and mature OS data, as supported by high ESMO-MCBS and ASCO-VF scores[15].  
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238 The large proportion of trials containing mature OS data may be explained by the fact that 62% of demands concern  
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2 239 post-MA drugs, where final results are more legitimate to be found. Unlike the FDA’s accelerated approval  
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4 240 pathway, the French AEA does not require confirmatory trials to verify the drug’s clinical benefit and obtain  
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6 241 definitive approval. Manufacturers are therefore inclined to submit demands containing more mature OS data to  
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8 242 comply with HAS requirements. However, as the reform is still recent, it is possible that the trend will change and  
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10 243 that drugs with early clinical endpoints such as ORR or PFS will be candidates to obtain an AEA [26–28].  
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12 244 Using national medico-administrative databases, our study also unveiled, the patient benefiting from EA oncology  
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14 245 drugs and associated reimbursement costs. We observed a significant rise in the number of patients receiving AEA  
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16 246 treatments, with a six-fold increase between 2019 and 2022, accompanied by an increase in costs by ten-fold over  
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18 247 the period. This growing number of patients and treatment costs appears to be connected to the simultaneous  
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20 248 availability of new drugs under EA, as well as new indications for existing drugs now encompassing multiple  
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22 249 therapeutic areas, as also noticed in other countries[15,16,23]. However, the momentum of increase in number of  
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24 250 indications (figure 2) and patients treated (figure 5) was already discernible during the ATU period and appear to  
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26 251 be continuing since the reform. The EA reform has thus facilitated but cannot explain the expansion of innovations  
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28 252 into the market in oncology.  
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30 253 Questions however remain regarding the financial aspects and the organisational modalities of the reform. The  
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32 254 very significant increase in costs may appear worrying, although the reform aimed to control expenditure to ensure  
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34 255 the health care sustainability. Despite the great increase in the number of indications and patients treated, the trend  
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36 256 may be explained by the fact that drug price are freely fixed by the manufacturer during the AEA period. However,  
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38 257 the cost presented in figure 4 does not reflect the final expense for the French health system, as the laboratory will  
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40 258 pay discounts based on AEA sales and the final drug price negotiated. Consequently, the reform is too recent to  
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42 259 estimate the economic burden of AEA on drug expenditures, and it impact regarding the sustainability and the  
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44 260 financing of therapeutic innovations. However, it is essential to closely monitor the impact of the reform and assess  
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46 261 whether adjustments are needed to the current system of financing early access, as well as to the mechanism of  
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48 262 post-regulatory control through rebates. Questions also linger about the successful and long-time efficacy of the  
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50 263 system. As part of the EA agreement, laboratories must provide real-life data on the use, the effectiveness, the  
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52 264 side-effects and sometimes the quality of life to HAS and ANSM, offering complementary insights to trials. If the  
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54 265 usefulness of this data collection is not questioned, challenges regarding the methods, quality, and funding of real-  
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56 266 word data collection, which currently rely on hospital teams, are now being raised by French experts[29].  
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267 Despite these points of caution, the EA reform in France has allowed fast arrival for patients to a significant number  
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2 268 of therapeutic innovations. It concerns innovative medicines for unmet medical needs for serious and sometimes  
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4 269 rare cancers, and are supported by high quality methodology studies with a demonstrated added clinical benefit.  
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6 270 The French EA system therefore appears to offer insights for other countries seeking to support and accelerate  
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8 271 access to innovations in oncology[7].  
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11  
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13  
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17  
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19  
20  
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22

23 278 **Consent to participate:** Not applicable  
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25 279 **Consent for publication** : Not applicable  
26

27  
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29  
30 281 the Systeme National des Données de Santé (SNDS) but restrictions apply to the availability of these  
31  
32 282 data, which were used under license for the current study, and so are not publicly available. Indeed,  
33  
34 283 under French law and regulations, databases extracted from the Systeme National des Données de Santé  
35  
36 284 (SNDS) cannot be publicly available.  
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41 286 **Code availability:** Not applicable  
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43 287 **Authors' contributions : CREDIT Statement:** **Tess Martin:** Conceptualization, Data curation,  
44  
45 288 Methodology, Writing original draft, Writing-Reviewing. **Catherine Rioufol:** Conceptualization,  
46  
47 289 Methodology, Writing-Reviewing, **Bertrand Favier:** Conceptualization, Writing-Reviewing, **Nicolas**  
48  
49  
50 290 **Martelli:** Conceptualization, Writing-Reviewing, **Isabelle Madelaine:** Conceptualization, Writing-  
51  
52 291 Reviewing, **Christos Chouaid:** Methodology, Writing-Reviewing, **Isabelle Borget:**  
53  
54 292 Conceptualization, Data curation, Methodology, Writing-Reviewing.  
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295 **References**

- 1  
2 296 1. European Cancer Information System [Internet]. [cited 2023 Jul 31]. Available from:  
3 297 <https://ecis.jrc.ec.europa.eu/>  
4  
5  
6 298 2. International Agency for Research on Cancer. Cancer Tomorrow [Internet]. [cited 2023 Jul  
7 299 31]. Available from: <https://gco.iarc.fr/tomorrow/en>  
8  
9 300 3. Polkowska M, Ekk-Cierniakowski P, Czepielewska E, Wysoczański W, Matusiewicz W,  
10 301 Kozłowska-Wojciechowska M. Survival of melanoma patients treated with novel drugs:  
11 302 retrospective analysis of real-world data. *J Cancer Res Clin Oncol*. 2017;143:2087–94.  
12  
13  
14 303 4. Assié J-B, Corre R, Levra MG, Calvet CY, Gaudin A-F, Grumberg V, et al. Nivolumab  
15 304 treatment in advanced non-small cell lung cancer: real-world long-term outcomes within  
16 305 overall and special populations (the UNIVOC study). *Ther Adv Med Oncol*.  
17 306 2020;12:1758835920967237.  
18  
19  
20 307 5. Newton M, Stoddart K, Travaglio M, Troein P. EFPIA Patients W.A.I.T. Indicator 2022  
21 308 Survey.  
22  
23 309 6. Europe’s Beating Cancer Plan [Internet]. European Commission; 2021 [cited 2023 Jan 23].  
24 310 Available from: [https://primarysources.brillonline.com/browse/human-rights-documents-](https://primarysources.brillonline.com/browse/human-rights-documents-online/communication-from-the-commission-to-the-european-parliament-and-the-council;hrdhrd46790058)  
25 311 [online/communication-from-the-commission-to-the-european-parliament-and-the-](https://primarysources.brillonline.com/browse/human-rights-documents-online/communication-from-the-commission-to-the-european-parliament-and-the-council;hrdhrd46790058)  
26 312 [council;hrdhrd46790058](https://primarysources.brillonline.com/browse/human-rights-documents-online/communication-from-the-commission-to-the-european-parliament-and-the-council;hrdhrd46790058)  
27  
28  
29 313 7. Tarantola A, Otto MH, Armeni P, Costa F, Malandrini F, Jommi C. Early access programs  
30 314 for medicines: comparative analysis among France, Italy, Spain, and UK and focus on the  
31 315 Italian case. *Journal of Pharmaceutical Policy and Practice*. 2023;16:67.  
32  
33  
34 316 8. EMA. Support for early access [Internet]. European Medicines Agency. 2018 [cited 2023  
35 317 Aug 1]. Available from: [https://www.ema.europa.eu/en/human-regulatory/overview/support-](https://www.ema.europa.eu/en/human-regulatory/overview/support-early-access)  
36 318 [early-access](https://www.ema.europa.eu/en/human-regulatory/overview/support-early-access)  
37  
38  
39 319 9. France’s New Framework for Regulating Off-Label Drug Use | NEJM [Internet]. [cited  
40 320 2023 Jul 31]. Available from: <https://www.nejm.org/doi/full/10.1056/NEJMp1208347>  
41  
42 321 10. DGOS ;DGS. Autorisation d’accès précoce, autorisation d’accès compassionnel et cadre  
43 322 de prescription compassionnelle [Internet]. Ministère de la Santé et de la Prévention. 2023  
44 323 [cited 2023 Aug 3]. Available from: [https://sante.gouv.fr/soins-et-](https://sante.gouv.fr/soins-et-maladies/medicaments/professionnels-de-sante/autorisation-de-mise-sur-le-marche/article/autorisation-d-acces-precoce-autorisation-d-acces-compassionnel-et-cadre-de)  
45 324 [maladies/medicaments/professionnels-de-sante/autorisation-de-mise-sur-le-](https://sante.gouv.fr/soins-et-maladies/medicaments/professionnels-de-sante/autorisation-de-mise-sur-le-marche/article/autorisation-d-acces-precoce-autorisation-d-acces-compassionnel-et-cadre-de)  
46 325 [marche/article/autorisation-d-acces-precoce-autorisation-d-acces-compassionnel-et-cadre-de](https://sante.gouv.fr/soins-et-maladies/medicaments/professionnels-de-sante/autorisation-de-mise-sur-le-marche/article/autorisation-d-acces-precoce-autorisation-d-acces-compassionnel-et-cadre-de)  
47  
48  
49 326 11. French National Health Insurance. The proposals of the French National Health Insurance  
50 327 for 2024 [Internet]. 2023 [cited 2023 Jul 31]. Available from: [https://assurance-](https://assurance-maladie.ameli.fr/etudes-et-donnees/2023-rapport-propositions-pour-2024-charges-produits)  
51 328 [maladie.ameli.fr/etudes-et-donnees/2023-rapport-propositions-pour-2024-charges-produits](https://assurance-maladie.ameli.fr/etudes-et-donnees/2023-rapport-propositions-pour-2024-charges-produits)  
52  
53  
54 329 12. Autorisation d’accès précoce, autorisation d’accès compassionnel et cadre de prescription  
55 330 compassionnelle [Internet]. Ministry of Health and Prevention. 2023 [cited 2023 Jan 10].  
56 331 Available from: [https://solidarites-sante.gouv.fr/soins-et-](https://solidarites-sante.gouv.fr/soins-et-maladies/medicaments/professionnels-de-sante/autorisation-de-mise-sur-le-marche/article/autorisation-d-acces-precoce-autorisation-d-acces-compassionnel-et-cadre-de)  
57 332 [maladies/medicaments/professionnels-de-sante/autorisation-de-mise-sur-le-](https://solidarites-sante.gouv.fr/soins-et-maladies/medicaments/professionnels-de-sante/autorisation-de-mise-sur-le-marche/article/autorisation-d-acces-precoce-autorisation-d-acces-compassionnel-et-cadre-de)  
58 333 [marche/article/autorisation-d-acces-precoce-autorisation-d-acces-compassionnel-et-cadre-de](https://solidarites-sante.gouv.fr/soins-et-maladies/medicaments/professionnels-de-sante/autorisation-de-mise-sur-le-marche/article/autorisation-d-acces-precoce-autorisation-d-acces-compassionnel-et-cadre-de)  
59  
60  
61  
62  
63  
64  
65

- 334 13. Early access to medicinal products [Internet]. Haute Autorité de Santé. [cited 2023 Feb 2].  
1 335 Available from: [https://www.has-sante.fr/jcms/r\\_1500918/en/early-access-to-medicinal-](https://www.has-sante.fr/jcms/r_1500918/en/early-access-to-medicinal-)  
2 336 products  
3
- 4 337 14. Martinalbo J, Bowen D, Camarero J, Chapelin M, Démolis P, Foggi P, et al. Early market  
5 338 access of cancer drugs in the EU. *Ann Oncol*. 2016;27:96–105.  
6 339
- 7 339 15. Pham FY-V, Jacquet E, Taleb A, Monard A, Kerouani-Lafaye G, Turcry F, et al. Survival,  
8 340 cost and added therapeutic benefit of drugs granted early access through the French temporary  
9 341 authorization for use program in solid tumors from 2009 to 2019. *Int J Cancer*.  
10 342 2022;151:1345–54.  
11 343
- 12 343 16. Jacquet E, Kerouani-Lafaye G, Grude F, Goncalves S, Lorence A, Turcry F, et al.  
13 344 Comparative study on anticancer drug access times between FDA, EMA and the French  
14 345 temporary authorisation for use program over 13 years. *European Journal of Cancer*.  
15 346 2021;149:82–90.  
16 347
- 17 347 17. Avis et décisions sur les médicaments [Internet]. Haute Autorité de Santé. [cited 2023  
18 348 Aug 1]. Available from: [https://www.has-sante.fr/jcms/p\\_3281266/fr/avis-et-decisions-sur-](https://www.has-sante.fr/jcms/p_3281266/fr/avis-et-decisions-sur-les-medicaments)  
19 349 les-medicaments  
20 350
- 21 350 18. WHOCC - ATC/DDD Index [Internet]. [cited 2023 Aug 4]. Available from:  
22 351 [https://www.whocc.no/atc\\_ddd\\_index/](https://www.whocc.no/atc_ddd_index/)  
23 352
- 24 352 19. Scailteux L-M, Droitcourt C, Balusson F, Nowak E, Kerbrat S, Dupuy A, et al. French  
25 353 administrative health care database (SNDS): The value of its enrichment. *Therapies*.  
26 354 2019;74:215–23.  
27 355
- 28 355 20. HAS. Transparency Committee doctrine. 2020.  
29 356
- 30 356 21. Early access to medicinal products [Internet]. Haute Autorité de Santé. [cited 2023 Oct  
31 357 17]. Available from: [https://www.has-sante.fr/jcms/r\\_1500918/en/early-access-to-medicinal-](https://www.has-sante.fr/jcms/r_1500918/en/early-access-to-medicinal-)  
32 358 products  
33 359
- 34 359 22. Subbiah V, Wirth LJ, Kurzrock R, Pazdur R, Beaver JA, Singh H, et al. Accelerated  
35 360 approvals hit the target in precision oncology. *Nat Med*. 2022;28:1976–9.  
36 361
- 37 361 23. Trends in the approval of cancer therapies by the FDA in the twenty-first century | *Nature*  
38 362 *Reviews Drug Discovery* [Internet]. [cited 2023 Jul 27]. Available from:  
39 363 <https://www.nature.com/articles/s41573-023-00723-4>  
40 364
- 41 364 24. LEEM. Bilan économique 2021 des entreprises du médicament - Edition 2022 [Internet].  
42 365 [cited 2023 Aug 4]. Available from: [https://www.leem.org/publication/bilan-economique-](https://www.leem.org/publication/bilan-economique-2021-des-entreprises-du-medicament-edition-2022)  
43 366 2021-des-entreprises-du-medicament-edition-2022  
44 367
- 45 367 25. Agrawal S, Arora S, Amiri-Kordestani L, de Claro RA, Fashoyin-Aje L, Gormley N, et al.  
46 368 Use of Single-Arm Trials for US Food and Drug Administration Drug Approval in Oncology,  
47 369 2002-2021. *JAMA Oncology* [Internet]. 2022 [cited 2023 Jan 11]; Available from:  
48 370 <https://doi.org/10.1001/jamaoncol.2022.5985>  
49 371
- 50 371 26. Fashoyin-Aje LA, Mehta GU, Beaver JA, Pazdur R. The On- and Off-Ramps of Oncology  
51 372 Accelerated Approval. *New England Journal of Medicine*. 2022;387:1439–42.  
52 373  
53 374  
54 375  
55 376  
56 377  
57 378  
58 379  
59 380  
60 381  
61 382  
62 383  
63 384  
64 385  
65 386

373 27. Beaver JA, Pazdur R. “Dangling” Accelerated Approvals in Oncology. *N Engl J Med.*  
1 374 2021;384:e68.

3 375 28. Mushti SL, Mulkey F, Sridhara R. Evaluation of Overall Response Rate and Progression-  
4 376 Free Survival as Potential Surrogate Endpoints for Overall Survival in Immunotherapy Trials.  
5 377 *Clinical Cancer Research.* 2018;24:2268–75.

8 378 29. Renne M, Maquin G, Rosant D, Villiet M, Seron A. Feedback from a university hospital  
9 379 one year after the “simplified” reform of early and expanded access programm: a growing  
10 380 complexity for health professionals. *Journal de Pharmacie Clinique.* 2022;41:149–57.

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## 15 382 **Figure Legends**

18 383 Figure 1: Flow-Chart for Early Access approvals analysis

20 384 Figure 2: Number of distinct ATU/EA indications of oncology drugs used in real-world practice  
21  
22 385 (quarterly-month representation) from 2019 to 2022

24 386 Figure 3: Number of patients treated by an ATU/AEA oncology drug, per tumor localization and per  
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26 387 month

29 388 Figure 4: Reimbursement costs for ATU/AEA oncology drugs, per tumor localization and per month

31 389 Figure 5 : Number of patients treated with an early access oncology drug according to their regulatory  
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33 390 status (ATU/EA/Mixed status) and per month

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## 38 392 **Figures captions**

41 393 **Fig. 1** Flow-Chart for Early Access approvals analysis

43 394 This flow chart illustrates the process of selecting early access authorization applications issued by the  
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45 395 HAS for the first part of the study.

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49 397 **Fig. 2** Number of distinct ATU/EA indications of oncology drugs used in real-world practice (quarterly-  
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51 398 month representation) from 2019 to 2022

54 399 This figure represents, by trimester, the number of oncology indications in early access, associated with  
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56 400 hospital prescriptions, between 2019 and 2022 found in the real-world database of the SNDS.

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402 **Fig.3** Number of patients treated by an ATU/AEA oncology drug, per tumor localization and per month

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2 403 This figure represents the number of patients treated with a molecule for an oncology indication in early  
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4 404 access, by tumor location and per month between 2019 and 2022. The data is derived from the real-  
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6 405 world database of the SNDS.

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11 407 **Fig. 4** Reimbursement costs for ATU/AEA oncology drugs, per tumor localization and per month

12  
13 408 This figure represents the reimbursement costs associated treated for early access treatments in  
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15 409 oncology, by tumor location and per month between 2019 and 2022. The data is derived from the real-  
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17 410 world database of the SNDS.

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22 412 **Fig. 5** Number of patients treated with an early access oncology drug according to their regulatory status

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24 413 (ATU/EA/Mixed status) and per month

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26 414 This figure represents the number of patients treated with an early access oncolodry drug according to  
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28 415 their refulatory status : ATU, Early access or mixed status. Of note, the mixed status corresponds to the  
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30 416 drugs that were able to directly transition from the ATU status to the early access status at the time of  
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32 417 the reform (July 2021).

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38 419 **Supplementary captions (submitted in a editable format separately)**

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40 420 **Supplementary Table 1:** List of drugs and related-indications granted with AE in oncology (solid  
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42 421 oncology and onco-hematology) between 07/01/2021 and 31/12/2022

43  
44 422 This table provides a list of early access authorizations granted by the National Health Authority since  
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46 423 the implementation of the early access reform (07/01/2021) and up to 12/21/20222, by molecule and by  
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48 424 indication.

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427 **List of Tables**

428 **Table 1: Characteristics of oncology drugs with an early access decision**

	Early access decision granted (n=39)	Early access decision denied (n=7)
<b>Characteristics of the drugs - Therapeutic class</b>		
<b>Radiopharmaceuticals</b>		
Diagnostic radiopharmaceuticals	1 (3%)	0 (0%)
Therapeutic radiopharmaceuticals	1 (3%)	0 (0%)
<b>Antineoplastic agents</b>		
Alkylating agents	1 (3%)	0 (0%)
Antimetabolites	1 (3%)	0 (0%)
Antineoplastic cell and gene therapy	6 (15%)	0 (0%)
Monoclonal antibodies and antibody drug conjugates	18 (46%)	2 (29%)
Other antineoplastic agents	5 (13%)	0 (0%)
Protein kinase inhibitors	6 (15%)	5 (71%)
<b>Cancer situation</b>		
<b>Solid tumors</b>		
Localized situation, adjuvant	3 (8%)	2 (29%)
Localized situation, neo adjuvant	1 (3%)	0 (0%)
Metastatic situation, 1st line	9 (23%)	1 (14%)
Metastatic situation, 2nd line	9 (23%)	3 (43%)
Metastatic situation, > 3 lines	4 (10%)	0 (0%)
<b>Hematological malignancies</b>		
1st line	1 (3%)	0 (0%)
2nd line	7 (18%)	1 (14%)
> 3 lines	5 (13%)	0 (0%)
<b>Characteristics of clinical trials</b>		
<b>Development phase</b>		
I, I/II	7 (18%)	2 (29%)
II	7 (18%)	2 (29%)
III	26 (67%)	3 (43%)
<b>Study type</b>		
<b>Comparative study</b>		
Direct comparison	27 (69%)	3 (43%)
Indirect comparison	0 (0%)	1 (14%)
Basket trial	1 (2%)	0 (0%)
<b>Non comparative study</b>		
Randomization	12 (31%)	3 (43%)
Randomized study	27 (69%)	3 (43%)
Non randomized study	12 (31%)	4 (57%)
<b>Double blind study</b>		
Yes	10 (26%)	0 (0%)
No	29 (74%)	7 (100%)
<b>Comparator</b>		
Clinically relevant comparator	20 (51%)	3 (43%)

Placebo or supportive care	7 (18%)	1 (14%)
NA <sup>a</sup>	12 (31%)	3 (43%)
<b>Primary Endpoint</b>		
Overall survival (OS)	11* (28%)	0 (0%)
Overall response rate (ORR)	11*(28%)	5 (71%)
Progression free survival (PFS)	11* (28%)	0 (0%)
Other	9*(23%)	2 (29%)
<b>Exploration of OS</b>		
OS as primary endpoint or co-primary endpoint	11 (28%)	0 (0%)
OS as secondary endpoint	25 (64%)	6 (86%)
Indirect comparison	0 (0%)	1 (14%)
Non included in the statistical analysis plan	3 (8%)	0 (0%)
<b>Maturity of OS data</b>		
Mature OS data	16 (41%)	0 (0%)
Non mature OS data	19 (49%)	7 (100%)
NA	4 (10%)	0 (0%)

<sup>a</sup>Non comparative studies

\*\*The total sum exceeds 39 final early access decisions related to the presence of co-primary endpoints



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7 **1 Impact of Early Access Reform on Oncology Innovation in France: Approvals, Patients, and**  
8 **Costs**

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10 3 Tess Martin<sup>1,2</sup>, Catherine Rioufol<sup>3,4</sup>, Bertrand Favier<sup>5</sup>, Nicolas Martelli<sup>1,2</sup>, Isabelle Madelaine<sup>6</sup>,  
11 4 Christos Chouaid<sup>7,8</sup>, Isabelle Borget<sup>9,10</sup>

12  
13 5 Affiliations:

14 6 <sup>1</sup>Pharmacy Department, Georges Pompidou European Hospital, AP-HP, 20 Rue Leblanc, 75015, Paris,  
15 7 France.

16 8 <sup>2</sup>Paris-Saclay University, GRADES, Faculty of Pharmacy, 17 Av. des Sciences, 91400 Orsay, France.

17 9 <sup>3</sup>Pharmacy Department, Lyon Sud Hospital, Hospices Civils de Lyon, Lyon, France.

18 10 <sup>4</sup>EA3738, CICLY, UCBL1, Lyon, France

19 11 <sup>5</sup>Centre Léon Bérard, Pharmacy Department, 28 rue Laennec, 69008 Lyon, France

20 12 <sup>6</sup>Pharmacy Department, Saint-Louis Hospital, AP-HP, 1 avenue Vellefaux 75010 Paris, France, Vice  
21 13 president of Société Française de Pharmacie Oncologique (SFPO)

22 14 <sup>7</sup>Service de Pneumologie, CHI Créteil,

23 15 <sup>8</sup>Inserm U955, UPEC, IMRB, Créteil France

24 16 <sup>9</sup>Gustave Roussy, Biostatistics and Epidemiology Office, Université Paris-Saclay, Villejuif, France

25 17 <sup>10</sup>Inserm, Université Paris-Saclay, CESP U1018, Oncostat, labeled Ligue Contre le Cancer, Villejuif,  
26 18 France

27 19 **Corresponding author:** Tess Martin

28 20 Paris-Saclay University, GRADES, Faculty of Pharmacy, 17 Av. des Sciences, 91400 Orsay, France.

29 21 Tel: +33156092575

30 22 E-mail: [tess.martin@universite-paris-saclay.fr](mailto:tess.martin@universite-paris-saclay.fr)

31 23 **Short Title : Impact of Early Access Reform on Oncology Innovation in France**

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36 28 materials discussed in this manuscript..

## Abstract

### Background

~~An ambitious reform of the Early Access (EA) process was set up in July 2021 in France, aiming to simplify procedures and accelerate access of innovative drugs. An ambitious reform of the Early Access (EA) process was implemented in France in July 2021.~~

### Objective

This study analyzes the characteristics of oncology drug approvals through the EA process, and its impact in real-life data for oncology patients.

### Methods

The number and characteristics of EA demands concerning oncology drugs submitted to the National Health Authority (HAS) were reviewed until December 31, 2022. A longitudinal retrospective study on patients treated with an EA oncology drug between January 1, 2019, and December 31, 2022 was also performed using the French Nationwide claims database (SNDS) to assess the impact of the reform in number of indications, patients and costs.

### Results

Among 110 published decisions, HAS granted 88 (80%) EA indications within 70 days of assessment on average, including 46 (52%) in oncology (67% in solid tumors and 33% in hematological malignancies). Approved indications were mostly supported by randomized phase III trials (67%), whereas refused EA relied more on non-randomised (57%) trials. Overall survival was the primary endpoint of 28% of EA approvals versus none of denied EA. In the SNDS data, the annual number of patients with cancer treated with an AEA drug increased from 3,137 patients in 2019 to 18,341 in 2022 (+484%), whereas the number of indications rose from 12 to 62, mainly in oncohematology (n=17), lung (n=12), digestive (n=9) and breast cancer (n=9). Reimbursement costs for EA treatments surged from €42 to €526 million (+1159%).

### Conclusion

The French EA reform contributed to enabling rapid access to innovations in a wide range of indications for oncology patients. However, the findings highlight ongoing challenges in financial sustainability, warranting continued evaluation and adjustments.

### Key points:

- The early access reform in France has enabled rapid access to innovation, particularly for oncology drugs.

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- Approved oncology drugs are mostly supported by high-level evidence studies ([phase III trials](#)) with mature overall survival data provided.
- The reform also led to a significant increase in the annual number of patients treated and reimbursement costs.

## MAIN TEXT

### 1. INTRODUCTION

Cancer is a major public health concern. In 2020, there were 2.7 million new cases in the European Union (EU) countries, leading to 1.3 million deaths[1]. Cancer-related deaths are expected to rise by over 24% by 2035, making it the leading cause of death[2], even with therapeutic innovations.

Drugs innovations, as targeted therapies, immunotherapies or CAR-T cells, have represented a significant breakthrough in the treatment of advanced cancer, significantly improving overall survival and patient's quality of life[3,4]. However, the process of reimbursement and drug pricing has become much more complex and longprolonged, attaining-taking 530-503 days on average after the EMA approval in France [5]. Since then, access to medicines in the EU has been accelerated, largely encouraged by the 'Europe's beating cancer' plan [6], and various schemes have emerged[7], such as the PRIME (priority medicines) programme for medicines to address unmet needs[8].

Early access programs (EAPs) are designed to provide patients access to medicines before their marketing authorization (MA) or during the national reimbursement & pricing process. In 1994, France was pioneer by implementing an EAP framework called authorization for temporary use (ATU)[9]. Due to successive modifications over time, the ATU system became however increasingly complex with six different pathways[10]. Concomitantly, expenditures related to innovative drugs (including those in ATU program) continued to rise significantly in France, exhibiting an annual growth rate of 54% between 2019 and 2022. Among these, oncology drugs have seen their costs more than triple over the past three years[11].

In July 2021, an ambitious reform of the French early access (EA) system was thus implemented with three main objectives : to simplify and harmonize procedures for EA to innovative drugs, allow patients faster access to drugs, and guarantee financial sustainability for the healthcare system[12]. Two pathways now exist: authorization for early access (AEA) and authorization for compassionate use (ACU). AEA concerns drugs in specific indications, aiming at treating serious, rare or debilitating disease, when all the following criteria are met: (i) in exceptional circumstances, (ii) no appropriate treatment exists, (iii) treatment cannot be postponed, (iv) efficacy and safety of the drug are highly presumed according to clinical trials and (v) the drug is presumed innovative in regards to a possible clinically meaningful comparator. AEA is applicable both to drugs in "Pre-MA" EA (before MA by EMA) or in "Post-MA" EA (MA is approved by EMA that not yet reimbursed/priced)[13]. Conversely, ACU eovers allows, the use of drugs without MA indications in France to treat severe or rare diseases when there is no appropriate treatment available, the patient cannot be enrolled in a clinical trial, and the implementation of

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treatment cannot be delayed. This applies to drugs not intended for registration or marketing. For example, EA has been granted for therapeutic innovations such as CAR T cell therapy and antibody drug conjugates for severe solid tumors and hematologic malignancies. Additionally, compassionate use has been granted for certain drugs already on the market but lacking marketing authorization for specific indications, such as dapsone for the treatment of autoimmune bullous dermatosis, drugs not intended to be registered or marketed.

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. Regarding financing for EA pathway, the drug is provided to healthcare institutions/hospitals at a price freely fixed by the manufacturer and communicated to the Economic Committee for Healthcare Products (CEPS). However, two types of rebates are applied afterwards: annual rebates based on the net invoiced turnover to healthcare institutions/hospitals, following a progressive scale set by decree. These rebates can be increased if the manufacturer fails to adhere to the terms of the early access agreement. Additionally, there are "unwinding" rebates based on the final negotiated price with the CEPS.

At the European level, various models of early access to medicines have also emerged. Spain regulates EAPs under Royal Decree 1015/2009, mainly nominal-based but with some cohort-based options like compassionate use. The UK's Early Access to Medicines Scheme (EAMS) covers pre-MA drugs for all trial-eligible patients, offered as either nominal or cohort-based. In Italy, multiple lists oversee early access and off-label use, including Law 648/96, Well-Established Use, and the 5% Fund. While Italy has shown generosity in implementing EAPs, it faces challenges due to mixed approaches combining early access with off-label use. The comparative study of these different early access systems has led researchers to consider the French EA reform as a potential model for harmonizing different European EAP. Some experts now consider the French EA reform as a potential model for harmonizing different European EAPs[7,13,14]. However, there is currently insufficient data assessing the impact in terms of drug approvals and number of treated patients in France, and no economic data is available since the EA reform[7,15,16]. This study aims to review the first 18 months of the reform, focusing on oncology (including hematological malignancies) drugs attending following an EAE demand AEA decision. The objectives were to analyse the characteristics of oncology drug approvals through the new AEA process and to evaluate the

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7 126 impact of the reform in real-life, in terms of number of indications, number of treated patients and costs, using the  
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9 127 nationwide claims database.

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12 129 **2. MATERIAL AND METHODS**  
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14 130 The present study follows a two-step approach. First, it used the National Health Authority data to identify and  
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16 131 analyse the characteristics (number, acceptance rate, delay for decision, tumor type, methodological issues of the  
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18 132 trial) of the AEA demands related to oncology drugs since the reform (July 1, 2021). Secondly, a longitudinal  
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20 133 study using data from the French Nationwide claims reimbursement database (SNDS) from 2019 to 2022 was  
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22 134 performed to evaluate the impact of the AEA reform in real-life conditions, in terms of number of drugs/indications  
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24 135 used, number of patients treated and reimbursement costs.

25 136 **2.1 Number and characteristics of drug demands to the AEA pathway**  
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27 137 All the AEA demands submitted to the HAS since the reform (July 1, 2021) until December 31, 2022 were  
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29 138 identified and reviewed. Given that HAS is now ~~responsive~~ responsible for of the AEA decisions, all the  
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31 139 information's regarding the corresponding demands are now available on the HAS website[17]. It included  
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33 140 information's regarding the drug, the claimed indication, the eligibility criteria to AEA program, the pivotal data  
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35 141 supporting the demand, the decision (approval/failure) and it reasons, and the submission and decision dates. Note  
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37 142 that these dossiers are presented by indication (rather than by drug), as authorization and reimbursement occur on  
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39 143 a per-indication basis.

40 144 For oncology (solid tumors and hematological malignancies) indications, we collected the drug's name,  
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42 145 therapeutic class (using WHO Anatomical Therapeutic Chemical classification[18]), the decision, and the time  
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44 146 between submission and decision. Data related on the methodology of the main trial supporting the EA demand  
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46 147 (phase, design, comparator, primary endpoint, presence of overall survival (OS) data and OS maturity if provided)  
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48 148 were also collected and compared between approval and failure decisions. Combination therapies that submitted  
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50 149 two similar demands were counted as a single one (n=4). Three demands for indication renewals with no significant  
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52 150 modification were excluded, as well as one demand concerning an antidote (glucarpidase), considering it has no  
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54 151 anti-tumor effect. Figure 1 presents the flowchart of the selected demands.

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57 153 **2.2 Real-word data on patients receiving an EA drug**  
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59 154 The second part of our analysis aimed to quantify the impact of the AEA reform in real life conditions, regarding  
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61 155 the number of drugs (or indications) administered, the number of patients treated by an EAE drug and their costs  
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in France. To do that, we performed an observational retrospective longitudinal study using the nationwide claims database (SNDS) between January 1, 2019, and December 31, 2022. The SNDS database contains claims data for more than 99% of the French population, covering both hospital and community care and both the public and private sectors[19]. The SNDS uses a unique and anonymous patient identifier, so that individual patients can be followed over their lifetime. Regarding medicines, ATU/AE treatments administered or delivered at hospital are documented into the MEDATU/MEDAPAC database, including information<sup>1</sup> on the drug code (UCD, *unite commune de dispensation*), the indication code<sup>1</sup>, the anonymous patient identifier, the month and year of delivery and the reimbursement cost from the French National Health Insurance's perspective (in €), before discounts are applied. For each indication code identified, the molecule's name, reimbursement dates under ATU/EA pathway, therapeutic area and anatomical location can be retrieved using a Ministry of Health's file[10].

All ATU/EA drug deliveries between 1 January 2019 and 31 December 2022 corresponding to solid tumours and haematological malignancies indications were extracted from the MEDATU/MEDAPAC databases. Analysis was restricted to indications included in the AEA pathway (from 07/01/2021 to 12/31/2022) and certain ATU indications (cohort ATU, "post-ATU," indication extension ATU, and direct access post-MAA, which later merged to become AEA status, during the period from 01/01/2019 to 06/30/2021), excluding ACU indications. For the selected indications, the number of indications used, the number of (prevalent) patients treated and the costs were calculated monthly and annually, and presented both globally and by tumor localisation.

Of note, the sum of the number of patients treated monthly is not equal to the number of patients treated annually, since patients are generally treated over several months.

Statistics were descriptive. Data from the HAS website were collected in Excel<sup>®</sup> (Microsoft Office 2016), whereas analyses from the SNDS data were conducted using SAS<sup>®</sup> software version 9.4.

**3.RESULTS**

**3.1 Characteristics of drugs and demands approved under the AEA reform**

By December 31, 2022, 130 demands for AEA have been submitted by manufacturers to the HAS. Among the 110 decisions published, 54 (49%) concerned oncology indications (67% in solid tumors and 33% in hematological malignancies). Across all therapeutic areas, the HAS has granted 88 (80%) positive access decisions, while the acceptance rate for oncology/hematological malignancies indications is 85%. Oncology drugs that were approved

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<sup>1</sup> A code provided by the French ministry used to label the drug under ATU/EA pathway in an authorized indication.

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7 184 and their indication are listed in Supplementary Table 1. Another point is the speed in decisions, as HAS and  
8 ANSM have rendered them within 70 days on average [range: 47- 113], and in less than 90 days in 87% of cases.  
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10 186 Regarding therapeutic classes, 21 (46%) approvals concerned monoclonal antibodies and antibody-drug  
11 conjugates drugs, 7 (15%) concerned protein kinase inhibitors (16%) and 6 (13%) concerned CAR-T cells agents.  
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13 188 The methodological characteristics of the trials supporting the EA decisions are presented on Table 1, according  
14 if AEA was granted (n=39) or denied (n=7). Granted AEA were mostly supported by phase III trials (67%) that  
15 189 included a randomisation (69%), whereas refused AEA were mainly phase I or II trials (58%), mostly non-  
16 190 comparative (43%). The notion of comparator is important, as 51% of granted AEA had a clinically relevant  
17 191 comparator<sup>2</sup>. But trials *versus* placebo or supportive care were also accepted in 18% of cases, in accordance with  
18 192 the HAS methodological guide[21] that accepts them when justified, particularly for rare diseases or when no  
19 193 treatment exists. Regarding primary (or co-primary) endpoint, they were distributed among overall survival (OS,  
20 194 28%), progression free survival (PFS, 28%), overall response rate (ORR, 28%) or another endpoint (23%) for  
21 195 granted demands. OS was also explored as secondary endpoint in 25 (64%) of granted cases. Conversely, primary  
22 196 endpoints were mostly ORR (71%) or other endpoints (29%) but never OS or PFS for denied demands. To date,  
23 197 all demands having mature OS data (41% of cases) in a comparative trial were accepted, meaning that OS data  
24 198 remain a major endpoint, including for the EA process. For the 7 denied demands, the HAS considered that an  
25 199 appropriate treatment already existed in the indication (6/7), or/and that the drug was not presumed innovative  
26 200 (5/7).

### 3.2 Evolution of the number of indications, patients and cost for AEA oncology drugs

37 201 The figure 2 presents the evolution of the number of distinct ATU/EA indications of oncology drugs used in real-  
38 202 world practice from 2019 to 2022, by trimester. It showed that the number of indications strongly increased over  
39 203 the period, ranging from 12 ATU indications (7 for solid cancers and 5 for hematological malignancies) in 2019  
40 204 to 62 EA indications in 2022, predominantly in hematological malignancies (n=17), lung cancer (n=12), digestive  
41 205 cancer (n=9) and breast cancer (n=9). This may be explained by multiple extension of indications (like CAR-T  
42 206 cells in multiple myeloma or pembrolizumab in 4 indications (2 in breast, 1 in pancreatic and 1 in cervical cancers),  
43 207 the arrival of new therapeutic classes (2 indications for the trastuzumab deruxtecan in breast cancer and in digestive  
44 208 cancer or teclistamab), or the pursuit of treatment under EA reform.  
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51 <sup>2</sup> According to the definition of HAS transparency committee's doctrine, a clinically relevant comparator may be  
52 a medicinal product (active substance or placebo, with or without MA), a medical device, a procedure or any  
53 other non-medicinal therapy (or diagnostic method). It plays the same role in the therapeutic strategy as the  
54 new medicinal product and is aimed at the same patients.[20]

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7 211 As a possible consequence, the annual number of patients with cancer who were treated with an AEA drug strongly  
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9 212 increased from 3,137 patients in 2019 to 18,341 in 2022 (+484%). The figure 3 shows the evolution of the number  
10 213 of patients treated by an AEA drug in France, by month and by tumor localization. It reveals that the number of  
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12 214 patients treated monthly with an oncology AEA treatment has risen steadily, being multiplied by 20 over the  
13 215 period, from 326 in Jan 2019 to 6,800 in Dec 2022. It mainly concerned patients treated for breast (from 68 to  
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15 216 2,877 patients, +4131%) or lung cancers (from 84 to 650 patients, +674%). New localizations have also emerged  
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17 217 like digestive and urological cancers, with 866 and 619 patients in December 2022, respectively. Hemato-  
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19 218 oncology, which represented approximately half of the treated patients in January 2019 (168 patients), saw a  
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21 219 sevenfold increase in its number of patients (1251 patients in December 2022) and represents only 18% of patients  
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23 220 treated with an EA oncologic drug at the end of the study period.  
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25 221 Reimbursement costs also increase significantly, from 42 to 526 million (M) between 2019 and 2022 (+1159%).  
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27 222 In 2022, the higher reimbursement costs concerned treatments for hematological malignancies (180 M€), breast  
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29 223 cancer (159 M€), urology (68 M€), and lung cancer (64 M€). Figure 4 shows the evolution of monthly  
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31 224 reimbursement costs for AEA drugs in France by tumor localization.

#### 30 225 31 226 **4. DISCUSSION**

32 227 With 88 indications approved within 18 months, the French early access reform has allowed rapid access to  
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34 228 innovations with a high level of evidence and a regulatory simplification of the previous EA systems. More than  
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36 229 half of approvals concerned oncology indications, predominantly for solid tumors, notably targeted kinase-  
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38 230 inhibitors and immunotherapy. The same trend is found in the US where roughly one-quarter of accelerated-  
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40 231 approved drugs are precision medicines for treating solid tumors since 1992[22]. This trend highlights the fact that  
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42 232 specific classes of innovative products dominate the oncology treatment landscape, testifying to the accelerated  
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44 233 pace of innovation in this field[23]. With decisions delivered within 70 days on average, ANSM and HAS comply  
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46 234 with the regulatory deadline in 87% of cases. This is outstanding as it granted immediate access for AEA drugs to  
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48 235 patients. The AEA process is notably quicker than the current drug reimbursement process and the previous ATU  
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50 236 evaluation, which required 497-503 days[5][22] and 257 days[24], respectively. In addition, approved indications  
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52 237 were supported by high-quality methodological studies, with mostly phase III trials including direct comparison,  
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54 238 randomisation and OS as primary endpoint in nearly one-third of cases, underlining the continued significance of  
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56 239 OS results as pivotal requirement in the French context. This differs from FDA approach for cancer accelerated  
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58 240 approvals, whom often rely on ORR data from early trial or single-arm trial[25]. It is however in accordance with

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7 241 the French evaluation performed by the HAS for common drug reimbursement, which enhance drugs with  
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9 242 substantial clinical benefits supported by methodologically rigorous studies[13]. Previous studies also  
10 243 demonstrated that ATU programs were based on robust approvals characterized by substantial enhancements in  
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12 244 clinical benefit and mature OS data, as supported by high ESMO-MCBS and ASCO-VF scores[15].  
13 245 The large proportion of trials containing mature OS data may be explained by the fact that 62% of demands concern  
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15 246 post-MA drugs, where final results are more legitimate to be found. Unlike the FDA’s accelerated approval  
16 247 pathway, the French AEA does not require confirmatory trials to verify the drug’s clinical benefit and obtain  
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18 248 definitive approval. Manufacturers are therefore inclined to submit demands containing more mature OS data to  
19 249 comply with HAS requirements. However, as the reform is still recent, it is possible that the trend will change and  
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21 250 that drugs with early clinical endpoints such as ORR or PFS will be candidates to obtain an AEA [26–28].  
22 251 Using national medico-administrative databases, our study also unveiled, the patient benefiting from EA oncology  
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24 252 drugs and associated reimbursement costs. We observed a significant rise in the number of patients receiving AEA  
25 253 treatments, with a six-fold increase between 2019 and 2022, accompanied by an increase in costs by ten-fold over  
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27 254 the period. This growing number of patients and treatment costs appears to be connected to the simultaneous  
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29 255 availability of new drugs under EA, as well as new indications for existing drugs now encompassing multiple  
30 256 therapeutic areas, as also noticed in other countries[15,16,23]. However, the momentum of increase in number of  
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32 257 indications (figure 2) and patients treated (figure 5) was already discernible during the ATU period and appear to  
33 258 be continuing since the reform. The EA reform has thus facilitated but cannot explain the expansion of innovations  
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35 259 into the market in oncology.  
36 260 Questions however remain regarding the financial aspects and the organisational modalities of the reform. The  
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38 261 very significant increase in costs may appear worrying, although the reform aimed to control expenditure to ensure  
39 262 the health care sustainability. Despite the great increase in the number of indications and patients treated, the trend  
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41 263 may be explained by the fact that drug price are freely fixed by the manufacturer during the AEA period. However,  
42 264 the cost presented in figure 4 does not reflect the final expense for the French health system, as the laboratory will  
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44 265 pay discounts based on AEA sales and the final drug price negotiated. Consequently, the reform is too recent to  
45 266 estimate the economic burden of AEA on drug expenditures, and its impact regarding the sustainability and the  
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47 267 financing of therapeutic innovations. However, it is essential to closely monitor the impact of the reform and assess  
48 268 whether adjustments are needed to the current system of financing early access, as well as to the mechanism of  
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50 269 post-regulatory control through rebates.—Questions also linger about the successful and long-time efficacy of the  
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52 270 system. As part of the EA agreement, laboratories must provide real-life data on the use, the effectiveness, the

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side-effects and sometimes the quality of life to HAS and ANSM, offering complementary insights to trials. If the usefulness of this data collection is not questioned, challenges regarding the methods, quality, and funding of real-world data collection, which currently rely on hospital teams, are now being raised by French experts [29]. Despite these points of caution, the EA reform in France has allowed fast arrival for patients to a significant number of therapeutic innovations. It concerns innovative medicines for unmet medical needs for serious and sometimes rare cancers, and are supported by high quality methodology studies with a demonstrated added clinical benefit. The French EA system therefore appears to offer insights for other countries seeking to support and accelerate access to innovations in oncology[7].

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~~Under French law and regulations, databases extracted from the Systeme National des Données de Santé (SNDS) cannot be made available.~~

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**References**

1. European Cancer Information System [Internet]. [cited 2023 Jul 31]. Available from: <https://ecis.jrc.ec.europa.eu/>
2. International Agency for Research on Cancer. Cancer Tomorrow [Internet]. [cited 2023 Jul 31]. Available from: <https://gco.iarc.fr/tomorrow/en>
3. Polkowska M, Ekk-Cierniakowski P, Czepielewska E, Wysoczański W, Matuszewicz W, Kozłowska-Wojciechowska M. Survival of melanoma patients treated with novel drugs: retrospective analysis of real-world data. *J Cancer Res Clin Oncol.* 2017;143:2087–94.
4. Assié J-B, Corre R, Levra MG, Calvet CY, Gaudin A-F, Grumberg V, et al. Nivolumab treatment in advanced non-small cell lung cancer: real-world long-term outcomes within overall and special populations (the UNIVOC study). *Ther Adv Med Oncol.* 2020;12:1758835920967237.
5. Newton M, Stoddart K, Travaglio M, Troein P. EFPIA Patients W.A.I.T. Indicator 2022 Survey.
6. Europe's Beating Cancer Plan [Internet]. European Commission; 2021 [cited 2023 Jan 23]. Available from: <https://primarysources.brillonline.com/browse/human-rights-documents-online/communication-from-the-commission-to-the-european-parliament-and-the-council;hrdhrd46790058>
7. Tarantola A, Otto MH, Armeni P, Costa F, Malandrini F, Jommi C. Early access programs for medicines: comparative analysis among France, Italy, Spain, and UK and focus on the Italian case. *Journal of Pharmaceutical Policy and Practice.* 2023;16:67.

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8. EMA. Support for early access [Internet]. European Medicines Agency. 2018 [cited 2023 Aug 1]. Available from: <https://www.ema.europa.eu/en/human-regulatory/overview/support-early-access>
9. France's New Framework for Regulating Off-Label Drug Use | NEJM [Internet]. [cited 2023 Jul 31]. Available from: <https://www.nejm.org/doi/full/10.1056/NEJMp1208347>
10. DGOS ;DGS. Autorisation d'accès précoce, autorisation d'accès compassionnel et cadre de prescription compassionnelle [Internet]. Ministère de la Santé et de la Prévention. 2023 [cited 2023 Aug 3]. Available from: <https://sante.gouv.fr/soins-et-maladies/medicaments/professionnels-de-sante/autorisation-de-mise-sur-le-marche/article/autorisation-d-acces-precoce-autorisation-d-acces-compassionnel-et-cadre-de>
11. French National Health Insurance. The proposals of the French National Health Insurance for 2024 [Internet]. 2023 [cited 2023 Jul 31]. Available from: <https://assurance-maladie.ameli.fr/etudes-et-donnees/2023-rapport-propositions-pour-2024-charges-produits>
12. Autorisation d'accès précoce, autorisation d'accès compassionnel et cadre de prescription compassionnelle [Internet]. Ministry of Health and Prevention. 2023 [cited 2023 Jan 10]. Available from: <https://solidarites-sante.gouv.fr/soins-et-maladies/medicaments/professionnels-de-sante/autorisation-de-mise-sur-le-marche/article/autorisation-d-acces-precoce-autorisation-d-acces-compassionnel-et-cadre-de>
13. Early access to medicinal products [Internet]. Haute Autorité de Santé. [cited 2023 Feb 2]. Available from: [https://www.has-sante.fr/jcms/r\\_1500918/en/early-access-to-medicinal-products](https://www.has-sante.fr/jcms/r_1500918/en/early-access-to-medicinal-products)
14. Martinalbo J, Bowen D, Camarero J, Chapelin M, Démolis P, Foggi P, et al. Early market access of cancer drugs in the EU. *Ann Oncol*. 2016;27:96–105.
15. Pham FY-V, Jacquet E, Taleb A, Monard A, Kerouani-Lafaye G, Turcry F, et al. Survival, cost and added therapeutic benefit of drugs granted early access through the French temporary authorization for use program in solid tumors from 2009 to 2019. *Int J Cancer*. 2022;151:1345–54.
16. 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.
17. Avis et décisions sur les médicaments [Internet]. Haute Autorité de Santé. [cited 2023 Aug 1]. Available from: [https://www.has-sante.fr/jcms/p\\_3281266/fr/avis-et-decisions-sur-les-medicaments](https://www.has-sante.fr/jcms/p_3281266/fr/avis-et-decisions-sur-les-medicaments)
18. WHOCC - ATC/DDD Index [Internet]. [cited 2023 Aug 4]. Available from: [https://www.whocc.no/atc\\_ddd\\_index/](https://www.whocc.no/atc_ddd_index/)
19. 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.
20. HAS. Transparency Committee doctrine. 2020.

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21. Early access to medicinal products [Internet]. Haute Autorité de Santé. [cited 2023 Oct 17]. Available from: [https://www.has-sante.fr/jcms/r\\_1500918/en/early-access-to-medicinal-products](https://www.has-sante.fr/jcms/r_1500918/en/early-access-to-medicinal-products)
  22. Subbiah V, Wirth LJ, Kurzrock R, Pazdur R, Beaver JA, Singh H, et al. Accelerated approvals hit the target in precision oncology. *Nat Med*. 2022;28:1976–9.
  23. 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>
  24. 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>
  25. 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>
  26. Fashoyin-Aje LA, Mehta GU, Beaver JA, Pazdur R. The On- and Off-Ramps of Oncology Accelerated Approval. *New England Journal of Medicine*. 2022;387:1439–42.
  27. Beaver JA, Pazdur R. “Dangling” Accelerated Approvals in Oncology. *N Engl J Med*. 2021;384:e68.
  28. Mushti SL, Mulkey F, Sridhara R. Evaluation of Overall Response Rate and Progression-Free Survival as Potential Surrogate Endpoints for Overall Survival in Immunotherapy Trials. *Clinical Cancer Research*. 2018;24:2268–75.
  29. Renne M, Maquin G, Rosant D, Villiet M, Seron A. Feedback from a university hospital one year after the “simplified” reform of early and expanded access programm: a growing complexity for health professionals. *Journal de Pharmacie Clinique*. 2022;41:149–57.

#### Figure Legends

- Figure 1: Flow-Chart for Early Access approvals analysis
- Figure 2: Number of distinct ATU/EA indications of oncology drugs used in real-world practice (quarterly-month representation) from 2019 to 2022
- Figure 3: Number of patients treated by an ATU/AEA oncology drug, per tumor localization and per month
- Figure 4: Reimbursement costs for ATU/AEA oncology drugs, per tumor localization and per month

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Figure 5 : Number of patients treated with an early access oncology drug according to their regulatory status (ATU/EA/Mixed status) and per month

**Figures captions**

**Fig. 1** Flow-Chart for Early Access approvals analysis

This flow chart illustrates the process of selecting early access authorization applications issued by the HAS for the first part of the study.

**Fig. 2** Number of distinct ATU/EA indications of oncology drugs used in real-world practice (quarterly-month representation) from 2019 to 2022

This figure represents, by trimester, the number of oncology indications in early access, associated with hospital prescriptions, between 2019 and 2022 found in the real-world database of the SNDS.

**Fig.3** Number of patients treated by an ATU/AEA oncology drug, per tumor localization and per month

This figure represents the number of patients treated with a molecule for an oncology indication in early access, by tumor location and per month between 2019 and 2022. The data is derived from the real-world database of the SNDS.

**Fig. 4** Reimbursement costs for ATU/AEA oncology drugs, per tumor localization and per month

This figure represents the reimbursement costs associated treated for early access treatments in oncology, by tumor location and per month between 2019 and 2022. The data is derived from the real-world database of the SNDS.

**Fig. 5** Number of patients treated with an early access oncology drug according to their regulatory status (ATU/EA/Mixed status) and per month

This figure represents the number of patients treated with an early access oncology drug according to their regulatory status : ATU, Early access or mixed status. Of note, the mixed status corresponds to the

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7 432 drugs that were able to directly transition from the ATU status to the early access status at the time of  
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9 433 the reform (July 2021).

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13 435 **Supplementary captions (submitted in a editable format separately)**

14 436 **Supplementary Table 1:** List of drugs and related-indications granted with AE in oncology (solid  
15  
16 437 oncology and onco-hematology) between 07/01/2021 and 31/12/2022  
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18 438 This table provides a list of early access authorizations granted by the National Health Authority since  
19 439 the implementation of the early access reform (07/01/2021) and up to 12/21/20222, by molecule and by  
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7 443 **List of Tables**

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9 444 **Table 1: Characteristics of oncology drugs with an early access decision**

	<u>Early access decision granted (n=39)</u>	<u>Early access decision denied (n=7)</u>
<b>Characteristics of the drugs - Therapeutic class</b>		
<b>Radiopharmaceuticals</b>		
<u>Diagnostic radiopharmaceuticals</u>	<u>1 (3%)</u>	<u>0 (0%)</u>
<u>Therapeutic radiopharmaceuticals</u>	<u>1 (3%)</u>	<u>0 (0%)</u>
<b>Antineoplastic agents</b>		
<u>Alkylating agents</u>	<u>1 (3%)</u>	<u>0 (0%)</u>
<u>Antimetabolites</u>	<u>1 (3%)</u>	<u>0 (0%)</u>
<u>Antineoplastic cell and gene therapy</u>	<u>6 (15%)</u>	<u>0 (0%)</u>
<u>Monoclonal antibodies and antibody drug conjugates</u>	<u>18 (46%)</u>	<u>2 (29%)</u>
<u>Other antineoplastic agents</u>	<u>5 (13%)</u>	<u>0 (0%)</u>
<u>Protein kinase inhibitors</u>	<u>6 (15%)</u>	<u>5 (71%)</u>
<b>Cancer situation</b>		
<b>Solid tumors</b>		
<u>Localized situation, adjuvant</u>	<u>3 (8%)</u>	<u>2 (29%)</u>
<u>Localized situation, neo adjuvant</u>	<u>1 (3%)</u>	<u>0 (0%)</u>
<u>Metastatic situation, 1st line</u>	<u>9 (23%)</u>	<u>1 (14%)</u>
<u>Metastatic situation, 2nd line</u>	<u>9 (23%)</u>	<u>3 (43%)</u>
<u>Metastatic situation, &gt; 3 lines</u>	<u>4 (10%)</u>	<u>0 (0%)</u>
<b>Hematological malignancies</b>		
<u>1st line</u>	<u>1 (3%)</u>	<u>0 (0%)</u>
<u>2nd line</u>	<u>7 (18%)</u>	<u>1 (14%)</u>
<u>&gt; 3 lines</u>	<u>5 (13%)</u>	<u>0 (0%)</u>
<b>Characteristics of clinical trials</b>		
<b>Development phase</b>		
<u>I, I/II</u>	<u>7 (18%)</u>	<u>2 (29%)</u>
<u>II</u>	<u>7 (18%)</u>	<u>2 (29%)</u>
<u>III</u>	<u>26 (67%)</u>	<u>3 (43%)</u>
<b>Study type</b>		
<b>Comparative study</b>		
<u>Direct comparison</u>	<u>27 (69%)</u>	<u>3 (43%)</u>
<u>Indirect comparison</u>	<u>0 (0%)</u>	<u>1 (14%)</u>
<u>Basket trial</u>	<u>1 (2%)</u>	<u>0 (0%)</u>
<b>Non comparative study</b>		
<u>Randomization</u>		
<u>Randomized study</u>	<u>27 (69%)</u>	<u>3 (43%)</u>
<u>Non randomized study</u>	<u>12 (31%)</u>	<u>4 (57%)</u>
<b>Double blind study</b>		
<u>Yes</u>	<u>10 (26%)</u>	<u>0 (0%)</u>
<u>No</u>	<u>29 (74%)</u>	<u>7 (100%)</u>
<b>Comparator</b>		
<u>Clinically relevant comparator</u>	<u>20 (51%)</u>	<u>3 (43%)</u>

<u>Placebo or supportive care</u>	<u>7 (18%)</u>	<u>1 (14%)</u>
<u>NA<sup>a</sup></u>	<u>12 (31%)</u>	<u>3 (43%)</u>
<b>Primary Endpoint</b>		
<u>Overall survival (OS)</u>	<u>11* (28%)</u>	<u>0 (0%)</u>
<u>Overall response rate (ORR)</u>	<u>11*(28%)</u>	<u>5 (71%)</u>
<u>Progression free survival (PFS)</u>	<u>11* (28%)</u>	<u>0 (0%)</u>
<u>Other</u>	<u>9*(23%)</u>	<u>2 (29%)</u>
<b>Exploration of OS</b>		
<u>OS as primary endpoint or co-primary endpoint</u>	<u>11 (28%)</u>	<u>0 (0%)</u>
<u>OS as secondary endpoint</u>	<u>25 (64%)</u>	<u>6 (86%)</u>
<u>Indirect comparison</u>	<u>0 (0%)</u>	<u>1 (14%)</u>
<u>Non included in the statistical analysis plan</u>	<u>3 (8%)</u>	<u>0 (0%)</u>
<b>Maturity of OS data</b>		
<u>Mature OS data</u>	<u>16 (41%)</u>	<u>0 (0%)</u>
<u>Non mature OS data</u>	<u>19 (49%)</u>	<u>7 (100%)</u>
<u>NA</u>	<u>4 (10%)</u>	<u>0 (0%)</u>

<sup>a</sup>Non comparative studies

\*\*The total sum exceeds 39 final early access decisions related to the presence of co-primary endpoints

**Table 1: Characteristics of clinical trials of oncology drugs with an early access decision**

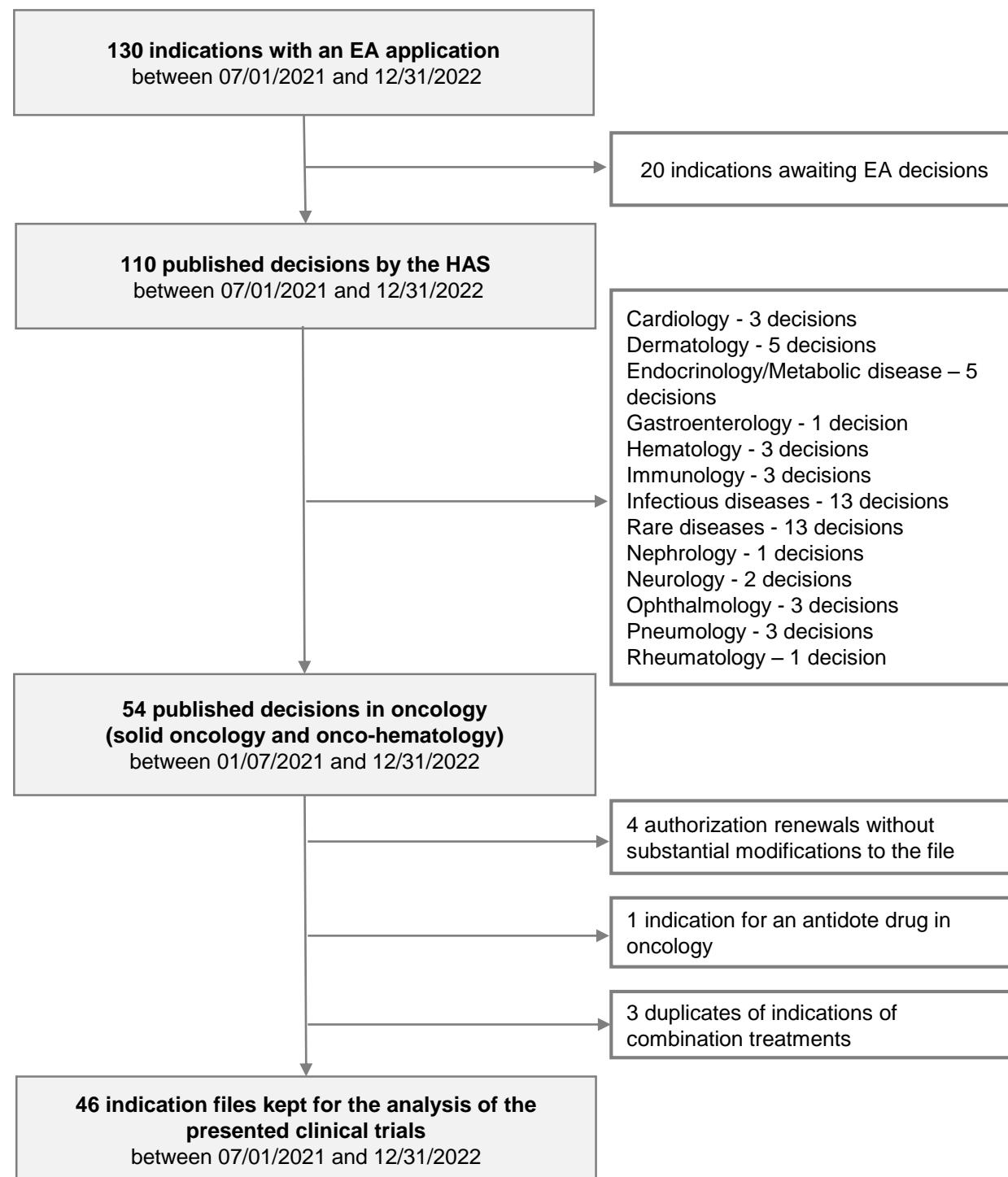
	Early-access decision granted (n=39)	Early-access decision denied (n=7)
<b>Development phase</b>		
<u>I, I/H</u>	<u>7 (18%)</u>	<u>2 (29%)</u>
<u>II</u>	<u>7 (18%)</u>	<u>2 (29%)</u>
<u>III</u>	<u>26 (67%)</u>	<u>3 (43%)</u>
<b>Study type</b>		
<u>Comparative study</u>		
<u>Direct comparison</u>	<u>27 (69%)</u>	<u>3 (43%)</u>
<u>Indirect comparison</u>	<u>0 (0%)</u>	<u>1 (14%)</u>
<u>Basket trial</u>	<u>1 (2%)</u>	<u>0 (0%)</u>
<u>Non-comparative study</u>		
<u>Randomization</u>		
<u>Randomized study</u>	<u>27 (69%)</u>	<u>3 (43%)</u>
<u>Non-randomized study</u>	<u>12 (31%)</u>	<u>4 (57%)</u>
<u>Double blind study</u>		
<u>Yes</u>	<u>10 (26%)</u>	<u>0 (0%)</u>
<u>No</u>	<u>29 (74%)</u>	<u>7 (100%)</u>
<b>Comparator</b>		
<u>Clinically relevant comparator</u>	<u>20 (51%)</u>	<u>3 (43%)</u>
<u>Placebo or supportive care</u>	<u>7 (18%)</u>	<u>1 (14%)</u>
<u>NA<sup>a</sup></u>	<u>12 (31%)</u>	<u>3 (43%)</u>

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Primary Endpoint		
Overall survival (OS)	11* (28%)	0 (0%)
Overall response rate (ORR)	11* (28%)	5 (71%)
Progression free survival (PFS)	11* (28%)	0 (0%)
Other	9* (23%)	2 (29%)
Exploration of OS		
OS as primary endpoint or co-primary endpoint	11 (28%)	0 (0%)
OS as secondary endpoint	25 (64%)	6 (86%)
Indirect comparison	0 (0%)	1 (14%)
Non-included in the statistical analysis plan	3 (8%)	0 (0%)
Maturity of OS data		
Mature OS data	16 (41%)	0 (0%)
Non-mature OS data	19 (49%)	7 (100%)
NA	4 (10%)	0 (0%)

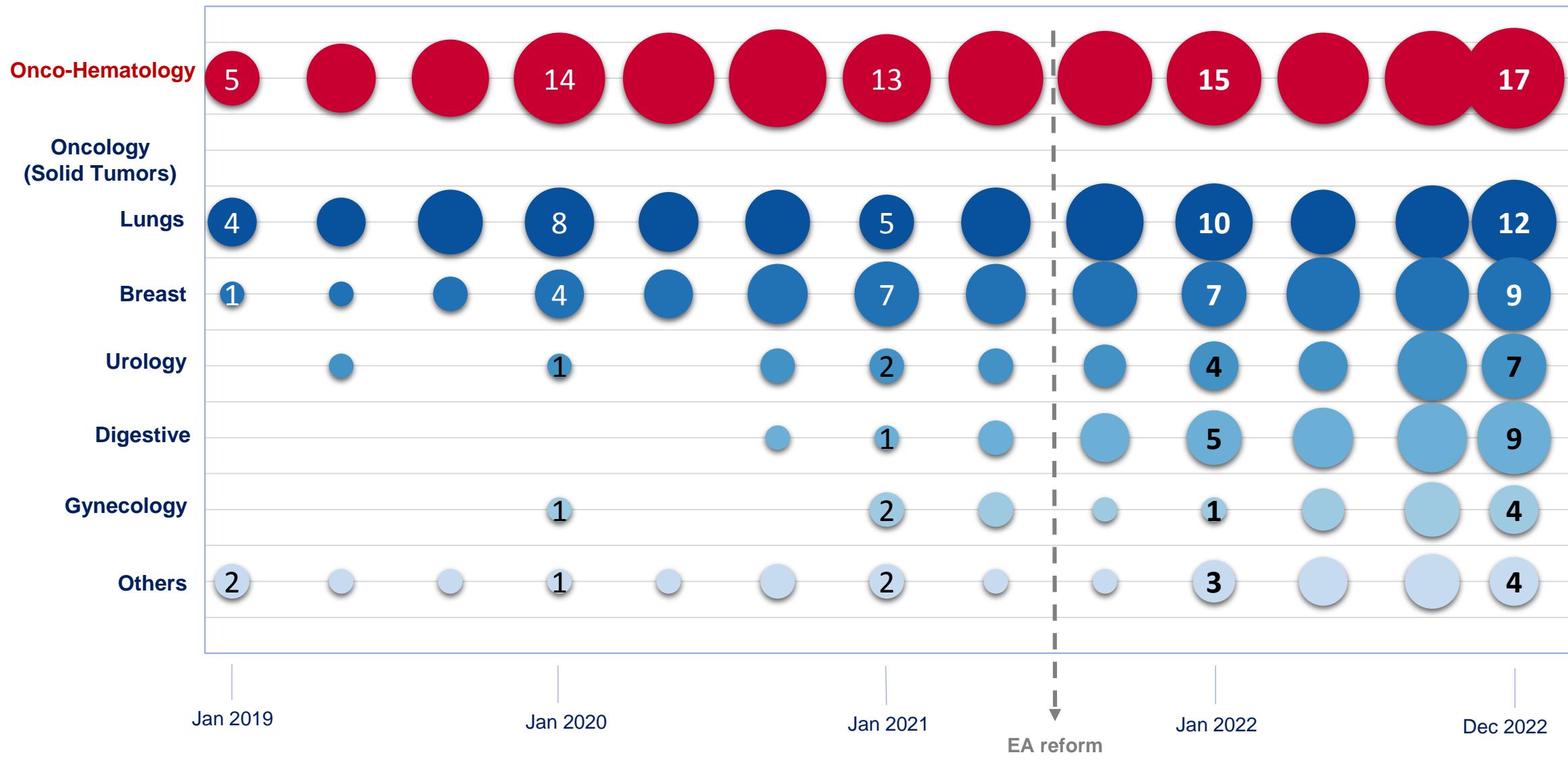
\*Non-comparative studies

\*\*The total sum exceeds 39 final early access decisions related to the presence of co-primary endpoints

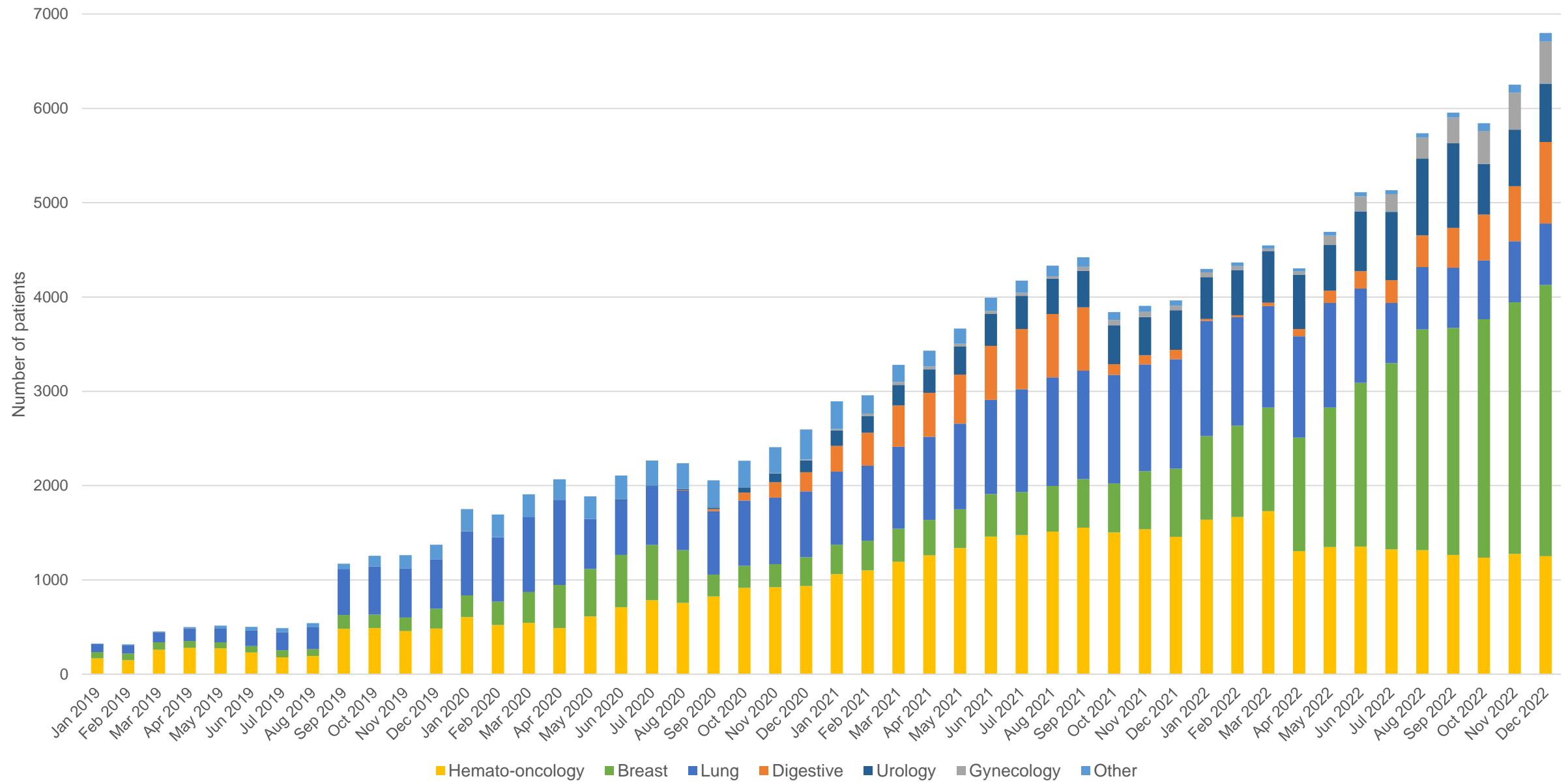


*EA = Early Access*

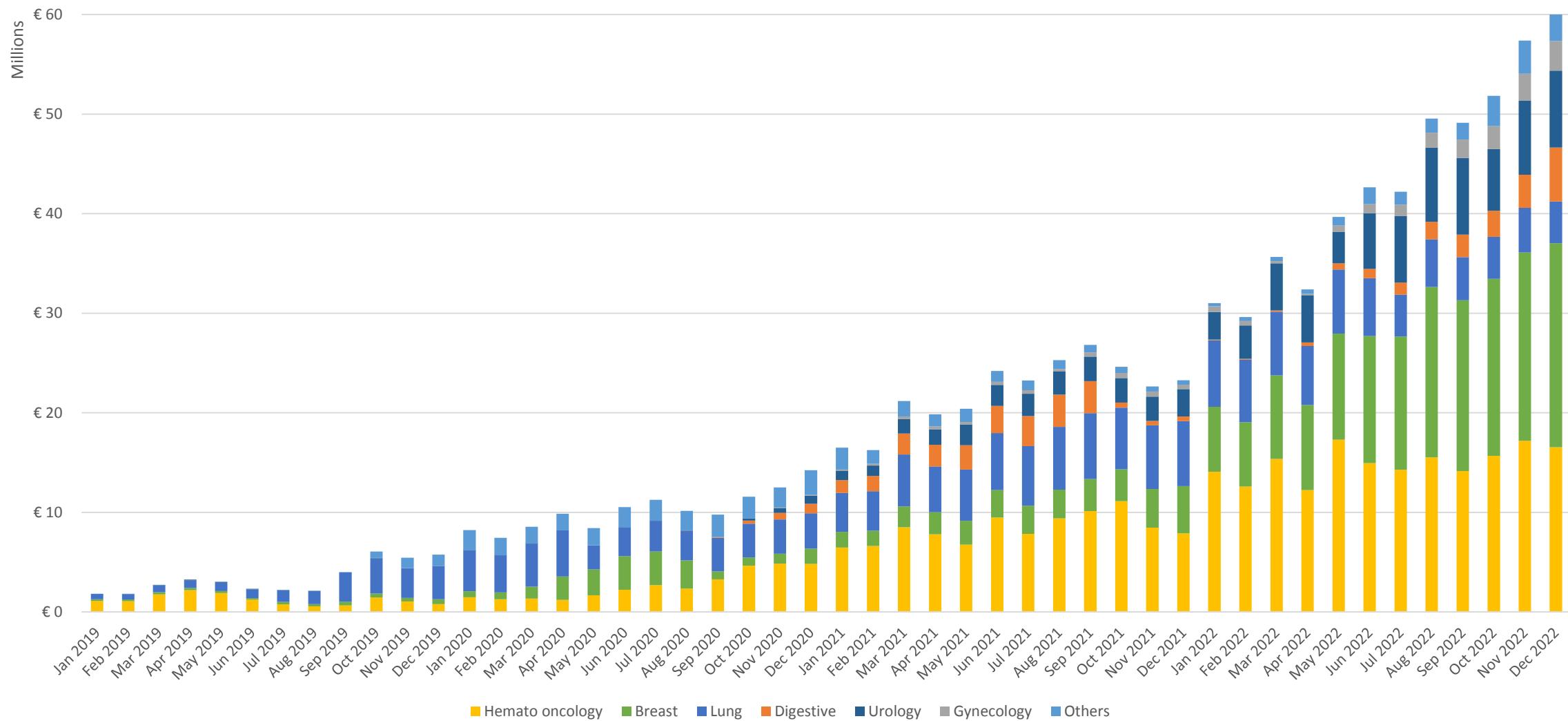
*HAS = Haute Autorité de Santé (National Health Authority)*



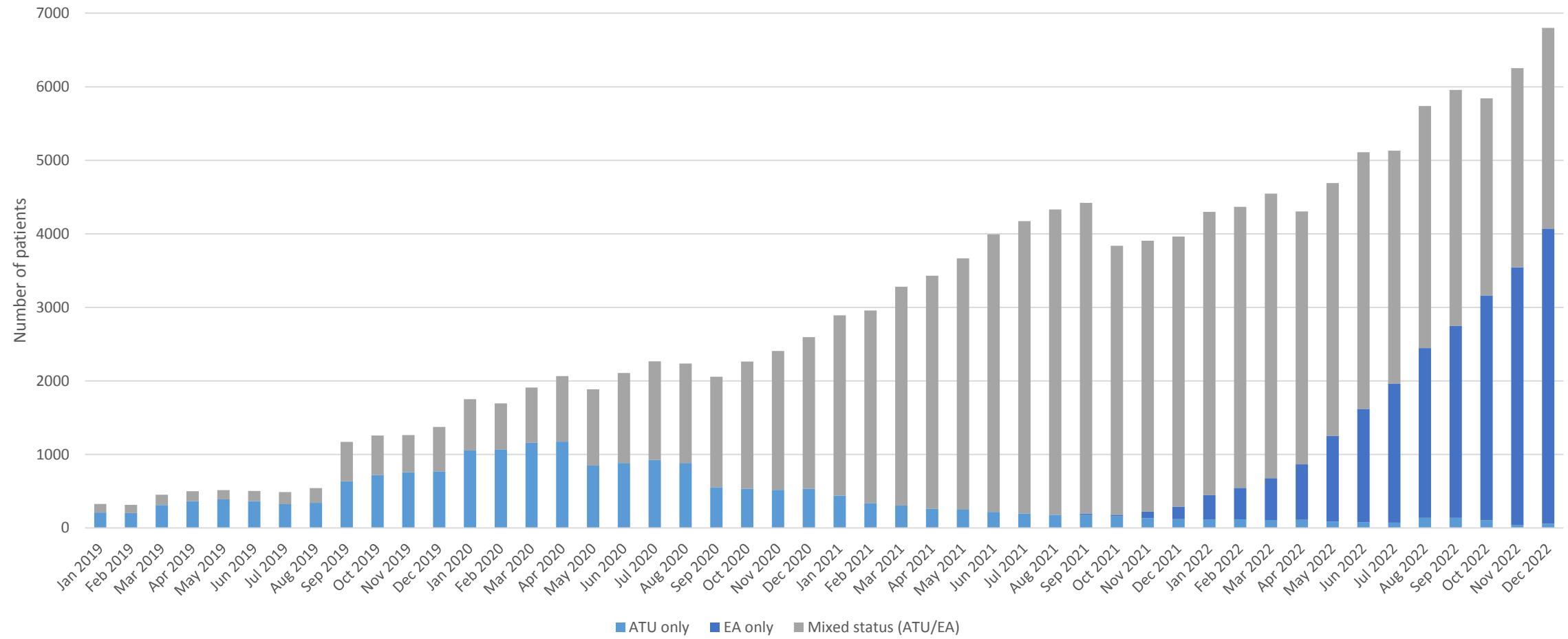
*EA reform = Early access reform*



*Others = Uveal Melanoma, Central Nervous System, Thyroid, Skin.*



*Others = Uveal Melanoma, Central Nervous System, Thyroid, Skin.*



EA = Early Access  
ATU = Authorization for use

Table 1: List of drugs and related-indications granted with AE in oncology (solid oncology and onco-hematology) between 07/01/2021 and 31/12/2022

Drugs	Indication granted with EA approval
[18F]PSMA-1007	[18F]PSMA-1007 is intended for use in positron emission tomography (PET). PET imaging following administration of Radelumin is indicated in patients experiencing biochemical recurrence of prostate cancer, initially treated radically, with a rise in serum prostate-specific antigen (PSA) levels. This medication is for diagnostic use only.
Amivantamab	In monotherapy, treatment of adult patients with advanced non-small cell lung cancer (NSCLC) harboring activating mutations of the epidermal growth factor receptor (EGFR) with exon 20 insertion, following failure of platinum-based therapy.
Asciminib	Monotherapy treatment for chronic myeloid leukemia with or without T315I mutation in patients previously treated with all available tyrosine kinase inhibitors on the market and who have relapsed, or in patients refractory or intolerant to tyrosine kinase inhibitors, or for whom treatment with one or more available tyrosine kinase inhibitors is contraindicated.
Avapritinib	Aggressive systemic mastocytosis (ASM), Systemic mastocytosis associated with haematological neoplasm (SM-AHN) or Mast cell leukaemia (MCL), after at least one systemic treatment.
Axicabtagene ciloleucel	Treatment for adult patients with relapsed or refractory follicular lymphoma, after at least three lines of systemic therapy.
	Treatment for adult patients with refractory or relapsed diffuse large B-cell lymphoma within 12 months after completion of first-line therapy, and eligible for salvage chemotherapy followed by intensified chemotherapy for hematopoietic stem cell transplantation.
Azacitidine	Maintenance therapy for adult patients with acute myeloid leukemia (AML) who have achieved complete remission (CR) or complete remission with incomplete count recovery (CRi) after induction therapy with or without consolidation treatment and who are not candidates (including patients who choose not to undergo) for hematopoietic stem cell transplantation (HSCT).
Ciltacabtagene autoleucel (cilta-cel)	Treatment for adult patients with relapsed and refractory multiple myeloma, who have received at least 3 prior treatments including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody, and whose disease has progressed during the most recent treatment.
Crizotinib	Treatment for relapsed or refractory ALK-positive anaplastic large cell lymphoma (ALCL), from the second line of therapy, in pediatric patients aged 6 years and older and young adults.
Durvalumab	Locally advanced or metastatic Bile Duct Cancer (in combination with cisplatin/gemcitabin).
Enfortumab vedotin	In combination with gemcitabine/cisplatin chemotherapy, first-line treatment for adult patients with advanced or metastatic biliary tract cancer.
Glucarpidase	Reduce toxic plasma concentrations of methotrexate in adults and children (from 28 days old) exhibiting delayed methotrexate elimination or at risk of methotrexate toxicity.
Idecabtagene vicleucel	Treatment of adult patients with relapsed and refractory multiple myeloma who have received at least three prior treatments, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody, and whose disease has progressed during the last treatment.

<b>Ipilimumab</b>	Indicated in combination with nivolumab, as first-line treatment, for adult patients with unresectable malignant pleural mesothelioma.
<b>Ivosidenib</b>	Monotherapy treatment for adult patients with unresectable or metastatic advanced cholangiocarcinoma harboring an isocitrate dehydrogenase 1 (IDH1) mutation and progressing after two lines of treatment for advanced unresectable and/or metastatic disease.
<b>Lenvatinib</b>	In combination with pembrolizumab, treatment for adult patients with advanced or recurrent endometrial cancer, whose disease progresses during or following prior platinum-based chemotherapy received at any stage and who are not eligible for curative surgery or radiotherapy.
<b>Lisocabtagene Maraleucel</b>	Treatment for adult patients with diffuse large B-cell lymphoma (DLBCL), high-grade B-cell lymphoma (HGBCL), or primary mediastinal large B-cell lymphoma (PMBCL), refractory or relapsed within 12 months following first-line treatment and eligible for hematopoietic stem cell transplantation (HSCT).
<b>Lutetium (177Lu) vipivotide tetraxetan (PSMA-617)</b>	Treatment for adults with progressive, metastatic, castration-resistant prostate cancer that overexpresses prostate-specific membrane antigen (PSMA) who have been treated with taxane chemotherapy and at least one anti-androgenic hormone therapy.
<b>Nivolumab</b>	As monotherapy in the adjuvant treatment of adult patients with residual disease after prior neoadjuvant radiochemotherapy for esophageal or esophagogastric junction cancer.
	In combination with a fluoropyrimidine-platinum-based chemotherapy regimen as first-line treatment for adult patients with advanced or metastatic HER2-negative gastric adenocarcinoma, esophagogastric junction adenocarcinoma, or esophageal cancer whose tumors express PD-L1 with a combined positive score (CPS) $\geq 5$ .
	As monotherapy for the adjuvant treatment of adult patients with muscle-invasive urothelial carcinoma (MIUC) at high risk of recurrence after complete resection, whose tumor cells express PD-L1 at a threshold of $\geq 1\%$ .
<b>Olaparib</b>	As monotherapy for the adjuvant treatment of adult patients with early-stage HER2-negative breast cancer at high risk who harbor a BRCA mutation and have received prior neoadjuvant or adjuvant chemotherapy.
<b>Pembrolizumab</b>	In combination with chemotherapy for the treatment of adult patients with locally recurrent or metastatic triple-negative breast cancer (TNBC) whose tumors express PD-L1 with a CPS $\geq 10$ and have not received prior systemic therapy for metastatic disease.
	In combination with chemotherapy as neoadjuvant treatment, followed by monotherapy after surgery as adjuvant treatment, in the treatment of adult patients with locally advanced, inflammatory, or early-stage triple-negative breast cancer at high risk of recurrence
	In combination with platinum-based and fluoropyrimidine chemotherapy, first-line treatment for adult patients with esophageal cancer or HER-2 negative adenocarcinoma of the gastroesophageal junction type I (Siewert classification), locally advanced unresectable, or metastatic, whose tumors express PD-L1 with a CPS $\geq 10$ .
	In combination with chemotherapy with or without bevacizumab, treatment for adult female patients with persistent, recurrent, or metastatic cervical cancer whose tumors express PD-L1 with a CPS $\geq 1$ .
<b>Ripretinib</b>	Treatment for adult patients with advanced gastrointestinal stromal tumor (GIST) who have previously been treated with at least three kinase inhibitors, including imatinib

Sacituzumab govitecan	Monotherapy treatment for adult patients with unresectable or metastatic triple-negative breast cancer who have received two or more prior lines of systemic therapy, including at least one in the advanced stage.*
Selpercatinib	Monotherapy treatment for adult and adolescent patients aged 12 years and older with advanced medullary thyroid cancer (MTC) harboring a RET gene mutation, requiring systemic treatment after prior treatment with cabozantinib and/or vandetanib.
Sotorasib	Monotherapy treatment for adult patients with advanced non-small cell lung cancer (NSCLC) harboring the KRAS G12C mutation, whose disease has progressed after at least one prior systemic therapy.
Tafasitamab	In combination with lenalidomide, followed by MINJUVI monotherapy, treatment for adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) who are not eligible for hematopoietic stem cell transplantation (HSCT)
Tebentafusp	Monotherapy for the treatment of adult patients with unresectable or metastatic uveal melanoma. HLA-A*02:01-positive.*
Teclistamab	Monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least three previous treatments, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody, and whose disease has progressed during the last treatment, when all therapeutic options have been exhausted (excluding cellular therapies), based on the advice of a multidisciplinary consultation meeting.
Témazolomide	Treatment for pediatric patients aged 12 months and older with refractory high-risk neuroblastoma or inadequate response to induction chemotherapy; and for pediatric patients aged 12 months and older with relapsed high-risk neuroblastoma after at least a partial response to induction chemotherapy followed by myeloablative therapy and stem cell transplantation
Tisagenlecleucel	Treatment for adult patients with follicular lymphoma after at least two lines of treatment: those with refractory disease, those who relapse during or within 6 months following the end of their maintenance treatment, or those who relapse after hematopoietic stem cell transplantation.
Trastuzumab deruxtecan	Treatment for adult patients with unresectable or metastatic HER2-positive breast cancer who have previously received anti-HER2 therapy. Specifically, monotherapy for adult patients with unresectable or metastatic HER2-positive breast cancer who have previously received anti-HER2 therapy and must have received prior treatment for locally advanced or metastatic disease or have experienced disease progression during adjuvant treatment or within six months after its completion. Monotherapy for adult patients with locally advanced or metastatic HER2-positive gastric or gastroesophageal junction adenocarcinoma who have previously received at least two lines of treatment including trastuzumab. Monotherapy for adult patients with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer who have received prior systemic therapy in the metastatic stage or have developed a recurrence of the disease during or within 6 months following the completion of adjuvant chemotherapy. Patients with hormone receptor-positive (HR+) breast cancer must also have received or be ineligible for hormone therapy.
Venetoclax	In combination with obinutuzumab, indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukemia (CLL) who are ineligible for BTK inhibitors and either ineligible for fludarabine-based treatment or have del(17p) and/or TP53 mutation.

\*Indications with early access renewals