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Old drug, new clinical use, no man's land for the indication: an awareness call from European experts

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INTRODUCTION

Licence holders of a new medical agent who apply for marketing authorisation in Europe have two choices: They may either apply to a national health authority (which limits authorisation to the authority's country) or choose the centralised procedure with the European Medicines Agency (EMA) to apply for authorisation for all countries belonging to the European Union (EU) as well as Liechtenstein, Iceland and Norway. For anticancer drugs, as well as several other categories, the central authorisation approach through EMA is compulsory since 2005.[1]

On application, EMA will launch a content-defined and timeline-defined verifying procedure (figure 1), which will lead to a recommendation. The agency has no legislative or other decisive power. EMA's recommendation will then be submitted to the European Commission, which will take the legal binding decision for marketing authorisation, based on EMA's recommendation. This is not synonymous but a precondition for pricing and reimbursement, as the latter remains within the competence of member states and their national and/or regional health authorities (with requirements, procedures and decisions varying according to each country). Having obtained marketing authorisation by the European Commission following EMA's recommendation, the drug's marketing authorisation holder (MAH) must thus proceed applying individually for pricing and reimbursement in each country he wishes to commercialise the drug.

The EMA marketing authorisation recommendation will precisely define the indication(s), the exact composition in active substance and excipients, patient and healthcare professional information and even packaging. It has to be renewed in regular intervals (usually every 5 years). There are costs for a company related to the submission of an application for marketing authorisation and for any other changes to it after approval, including for regular renewal. Cancer (as well as other) drug generics have an application procedure mainly based on pharmaceutical data and bioequivalence studies compared with the originator compound. This, again will lead to marketing authorisation for clearly defined indications in line with the originator compound.

A marketing authorisation is based on trial outcomes, mostly studied and reported by clinical researchers and investigators. However, only the drug licence holder will apply for authorisation as he will receive marketing authorisation after approval. Anticancer drugs having been authorised at a national level before 2005 (and thus restricted for use in one or some European countries only) may never be reconsidered for central approval through EMA due to commercial or other considerations, which depend on the licence holder (even though a generic may be applied for at EMA when the original was only nationally registered. Changes concerning the licence may occur once the drug is authorised, regarding either packaging, new side effects and precautions or more importantly new indications.[2] They require authorisation through a new, specific authorisation procedure, which the MAH must apply for. The procedure depends on the type of variation: EMA recognises 'type I variations' (minor, ie, packaging, excipients, units per blister), and 'type II variations', including, among others, new indications for the authorised drug.[3]

Application for a new indication (or a different posology) of a known and EMA authorised anticancer drug is a type II variation request. After the necessary documents have been submitted to and received by EMA,

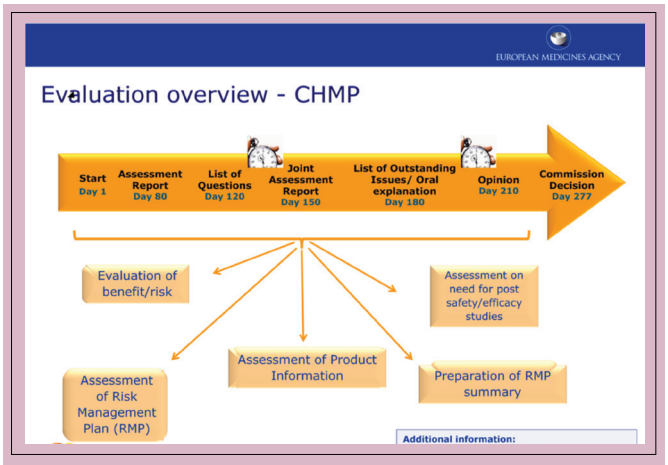

Figure 1 Procedure and timelines for first drug marketing approval by EMA. CHMP, Committee for Medicinal Products for Human Use. Source: ema.europa.eu

a 60-day evaluation period starts (figure 2). This period may be reduced, depending on urgency of the matter (particularly safety issues), or extended to 90 days for an extension of the indication. In case of a positive recommendation by EMA, a European Commission amendment of the initial approval follows with updates often on an annual basis (figure 3). In case of an orphan indication, specific procedures and documents are warranted.

In our awareness call, we provide clinical examples of 'old' anticancer drugs with expired patents for which 'new' clinical uses have emerged on the basis of scientifically robust, academia-led phase III clinical trials that provided proof of substantial patient benefit. In view of commercial availability of many generic versions of these therapeutics and since only the drug licence holder can apply for EMA authorisation, an awkward 'No Man's land' situation emerges for these drugs, when the licence holders have no financial incentive to apply for the new authorisation/indication. We also provide a similar 'orphan' example

Day	Action
Day 1	Start of evaluation
Day 36	Receipt of CHMP♯ Rapporteur's Assessment Report
Day 43^	Receipt of PRAC Rapporteur's Assessment Report
Day 47^	Comments by other PRAC members
Day 50	Comments by other CHMP members
Day 51^	Receipt of PRAC Rapporteur's updated Assessment Report*
Day 53	Receipt of CHMP♯ Rapporteur's updated Assessment Report*
Day 58^	PRAC outcome
Day 60	Adoption of the CHMP Opinion *[or Request for supplementary information]*

Figure 2 A 60-day procedure for variation II amendments. CHMP, Committee for Medicinal Products for Human Use; PRAC, Pharmacovigilance Risk Assessment Committee.Source (downloaded on 22.09.2019): ec.europa.eu https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-2/c_2013_2008/c_2013_2008_pdf/c_2013_2804

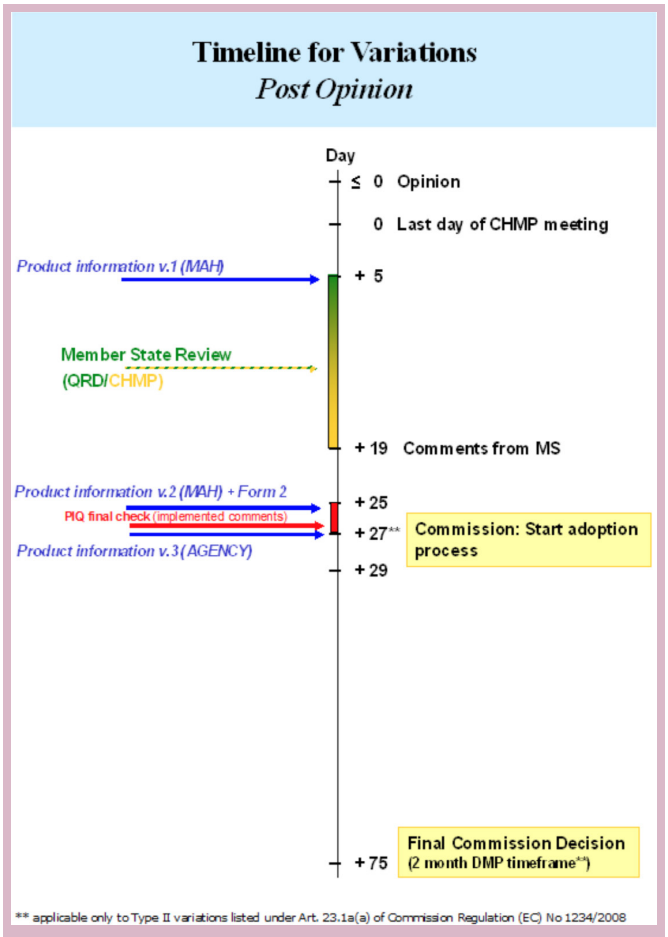

Figure 3 EU commission authorisation procedure and timeline for variation II changes after EMA recommendation. CHMP Committee for Medicinal Products for Human Use; DMP Development Medicinal Product; EC European Commission; EMA, European Medicines Agency; EU, European Union;MAH Market Authorization Holder; MS Member State; QRD Quality Review of Documents. MAH, Marketing Authorisation Holder; QRD, Quality Review of Documents, MS, Member State, DMP, Development Medicinal Product, EC, European Commission. Source (downloaded on 22.09.2019): ec.europa.eu https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-2/c_2013_2008/c_2013_2008_pdf/c_2013_2804

for a modified dosing regimen with potentially equal efficacy and lower cost of an on-patent therapeutic, which the licence holder likely has no interest to pursue. Finally, we propose that, in order for patients to access new and often more efficient use of 'old' drugs already approved in other indications, a new process of approval should be put in place by the regulators.

CLINICAL VIGNETTES

Adjuvant therapies in pancreatic cancer

Pancreatic cancer remains a dismal disease with a high mortality rate that goes hand to hand with its incidence and an overall 5-year survival rate less than 5%. Even for patients who are diagnosed early and undergo a curative resection, prognosis is poor with a 5-year survival rate of

about 20%.[4] Recently a phase III trial explored the efficacy of FOLFIRINOX (5-Fu, Leucovorine, Oxaliplatine, Irinotecan) in the adjuvant setting of resected patients with pancreatic cancer.[5] Following R0 or R1 resection, patients were randomised to receive either gemcitabine (1000 mg/m^2 on days 1, 8, and 15) every 4 weeks, or a modified FOLFIRINOX (mFOLFIRINOX) regimen every 2 weeks for 6 months. Demonstrating a significantly longer disease-free survival compared with gemcitabine (median DFS 21.6 vs 12.8 months, respectively, p<0.001) and the best overall survival (OS) ever observed in these patients (median OS 55 vs 35 months, 3-year survival rate of 63 vs 48% and 5-year survival of roughly 48 vs 28%), mFOLFIRINOX is currently recommended by the European Society of Medical Oncology (ESMO) guidelines as the first therapeutic option after resection of pancreatic cancer in selected and fit patients with an ESMO-Magnitude of Clinical Benefit Scale (MCBS) V.1.1 score: A.[6]

Irinotecan is a camptothecin semisynthetic analogue, originally manufactured by Pharmacia & Upjohn, extracted from the Camptotheca Acuminata tree; it inhibits topoisomerase I and results in single strand breaks during S phase that cannot be relegated at the presence of the drug. Oxaliplatin was licensed to Sanofi-Aventis in 1994 and causes cell death by preventing DNA replication and transcription, specifically through the formation of platinum-DNA adducts.[7] Fluoropyrimidines are antimetabolites that prevent DNA replication by inhibiting synthesis of thymidine, leading rapidly dividing cells to death due to lack of building blocks. The patents for irinotecan (Pfizer-CAMPTOSAR) and oxaliplatin (Sanofi Aventis-ELOXATIN) have expired in 2008 and 2016, respectively, and more than 33 generic formulations are currently licensed in the EU.[8]

For patients not fit for FOLFIRINOX, an effective adjuvant therapy has emerged from the ESPAC4 study.[9] A total of 732 patients who had undergone complete macroscopic resection for ductal adenocarcinoma of the pancreas (R0 or R1 resection) were randomly assigned to receive either six cycles of 1000 mg/m^2 gemcitabine alone weekly for 3 weeks or 1660 mg/m^2 oral capecitabine administered for 21 days, followed by 7 days rest gemcitabine and capecitabine (GEMCAP regimen). At a median follow-up of 43 months, the median OS for patients in the gemcitabine plus capecitabine group was 28.0 months (95% CI 23.5 to 31.5) compared with 25.5 months (22.7 to 27.9) in the gemcitabine group (HR 0.82, 95% CI 0.68 to 0.98, p=0.032). Estimated 5-year survival was 16.3% (10.2 to 23.7) for patients randomised to gemcitabine, and 28.8% (22.9 to 35.2) for patients randomised to gemcitabine plus capecitabine. As a result, adjuvant GEMCAP is considered by the ESMO guidelines the standard of care for patients with resected pancreatic cancer who are not fit for FOLFIRINOX (ESMO-MCBS A).[6] At the time ESPAC-4 data were publicly announced, Roche's Xeloda patent had expired (14 December 2013) and several capecitabine generics are commercially available.[8] Currently, neither capecitabine nor gemcitabine is indicated as adjuvant treatment for pancreatic cancer.[10]

Perioperative 5-fluorouracil, leucovorin, oxaliplatine and docetaxel (FLOT) therapy in resectable gastric cancer

Prognosis in patients with locoregional gastric cancer even after curative resection remains uncertain. However, the addition of perioperative chemotherapy has shown to improve OS and the rate of R0 resections. The MAGIC trial demonstrated that the perioperative combination of epirubicin, cisplatin, fluorouracil (ECF) improved progression-free survival (PFS) and OS over surgery alone and established the role of perioperative approach.[11]

The FLOT4 study was a phase 2/3 trial that randomised patients with gastric or gastro-oesophageal adenocarcinoma of clinical stage T2 or higher, node-positive (N+) or both,[12] to receive either three preoperative and three postoperative 3 week cycles of ECF/ECX (epirubicine, cisplatine, capecitabine) (control group) or four preoperative and four postoperative 2 week cycles of 50 mg/m^2 docetaxel, 85 mg/m^2 oxaliplatin, 200 mg/m^2 leucovorin and 2600 mg/m^2 fluorouracil as 24-hour infusion on day 1 (FLOT; experimental group). Median OS was superior in the FLOT group, 50 vs 35 months (HR 0.77, 95% CI 0.63 to 0.94; p=0.012). Median DFS was 18 months in the ECF/ECX group and 30 months in the FLOT group (HR 0.75; 95% CI 0.62 to 0.91; p=0.0036). Moreover, more patients underwent oncological surgery (336 (94%) vs 314 (87%); p=0.001) and achieved R0 resection (301 (85%) vs 279 (78%); p=0.0162 in the FLOT group. Regarding toxicity, grade 3 or 4 nausea, vomiting, thromboembolism and anaemia was more pronounced in the ECF/ECX group while more grade 3 or 4 events of infection, neutropenia, diarrhoea and neuropathy were observed in the FLOT group. The incidence of serious adverse events was similar in both groups, as well as the incidence of postoperative complications. Based on these data, the FLOT regimen is now considered the standard of care in the perioperative setting in the ESMO clinical practice guidelines, having received an ESMO-MCBS score of A.[13] Currently, there is no marketing authorisation of fluorouracil, oxaliplatin or docetaxel as part of the FLOT regimen by EMA. Separate approval has been gained for docetaxel and fluorouracil for use with the docetaxel, cisplatin, fluorouracil regimen in the metastatic setting. There is no indication for administration of oxaliplatin in patients with gastric cancer as suggested by the summary of product characteristics.

Modified postprandial low-dose abiraterone regimen in advanced prostate cancer

Abiraterone acetate, an androgen synthesis inhibitor, is one of the most broadly employed agents against metastatic prostate cancer. It gained EMA approval against metastatic castration resistant prostate cancer (CRPC) in 2011, having been shown to reduce risk of death by 34.5% compared with placebo, in the postchemotherapy setting,[14] and was later extended to chemotherapy naïve CRPC patients (57% combined death or disease progress

risk reduction vs placebo).[15] In 2018, abiraterone was further approved for high-risk hormone sensitive metastatic disease, based on the LATITUDE trial, where it was found superior to placebo in terms of OS, PFS and symptomatic relief, when added to the androgen-deprivation therapy.[16] In all of the above studies, abiraterone was used at the dose of its observed pharmacodynamic plateau, which is 1000 mg daily, after overnight fast, leading to its present global prescribing recommendations. Nonetheless, there is evidence that the bioavailability of abiraterone can be enhanced by fat-containing food intake.[17] In that setting, a 1:1 randomised, two arm phase II trial, compared the efficacy of the standard 1000 mg fasting abiraterone regimen, to an alternative one of abiraterone taken with a low fat meal at 250 mg per day in 72 CRPC patients.[18] The trial achieved its primary endpoint, as mean log prostate specific antigen (PSA) decrease at 12 weeks of treatment was −1.19 and −1.59 in the standard and low dose arm, respectively, establishing non-inferiority of the latter, according to the predefined protocol. Median PFS, a secondary endpoint, was 8.6 months in both treatment arms. Interestingly, testosterone and dehydroepiandrosterone (DHEA-S) concentrations were similarly decreased in both treatment arms. The above findings, if validated, suggest that an alternative abiraterone dosing regimen could be proved as safe and effective as the standard one, at ¼ of the currently employed dose. Notably, the abiraterone patent, currently owned by Janssen, expires in 2027. According to the regulations of the European Patent Office, medicament patenting does not preclude merely amending the dose of an already patented agent, provided that the safety, efficacy and novelty of the suggested altered regimen are scientifically and legally established.[19] On that basis, new patent claims of alternative abiraterone regimens could arise, even before the expiry date of the current dosing regimen patent.

REGULATORY ENVIRONMENT AND REIMBURSEMENT IN EUROPE

Greece

The Greek healthcare system is a mixed system of public–private provision of healthcare services. It consists of the National Health System (ESY), which comprises public hospitals, health centres and of the private sector, with numerous diagnostic centres, private hospitals and laboratories.[20] Healthcare is funded by the governmental budget (general taxation), by the recently unified Social Insurance Fund (employee-insured premiums with government subsidies) and by private expenditure.

Medicinal products require a prescription and follow approved EMA indications. Medications are reimbursed by a governmental agency (National Organisation for Healthcare Provisions, EOPYY), after evaluation and positive assessment by national Health Technology Assessment (HTA) bodies and definition of a price, with 100% state reimbursement for severe or life-threatening diseases (such as cancer).

Innovative, expensive anticancer targeted compounds, despite EMA and national HTA approval, require upload of an electronic petition with detailed patient and tumour data by the physician in a dedicated website. Following this, therapy approval and state reimbursement are issued within ten days. Use of any therapeutic outwith the EMA indication, expensive or inexpensive, has to be requested electronically via the dedicated website, with upload of patient/tumour data, and may be rejected. Consequently, 'old' inexpensive drugs with new clinical uses will not be reimbursed by EOPPY if administered outside the EMA indication.

Luxembourg

The Luxembourg healthcare system is entirely public, funded through the compulsory contributions of citizens/workers to the national health insurance. Healthcare is delivered mainly by public, but partially also private healthcare providers within a collective convention with the national health insurance. Reimbursement is granted for items listed within the convention and reimbursed according to fixed tariffs. Prescription drugs are reimbursed to patients according to the nationally fixed price with various degrees of patient contribution. All antineoplastic agents are fully covered by the public health insurance at no cost to the patient. Intravenous/injectable antineoplastic agents are exclusively available to the four national hospital pharmacies (and administered exclusively in one of their inpatient or outpatient clinics). With few exceptions, 'new' oral anticancer drugs are equally exclusively distributed by hospital pharmacies. Hospital pharmacies will receive a fixed sum for injectable chemotherapies per day of administration (no matter how expensive or complex the treatment protocol is), while some very expensive treatments are separately opposable. The same is true for most expensive oral targeted drugs.

National authorisation and pricing will come with automatic reimbursement approximately 6 months after EMA approval of new drugs. Once EMA approved, they can be used off-label at the discretion of the treating oncologists: Legally, the Medical Control Council of the national insurance agency could refuse reimbursement, but so far, the legal body has pragmatically decided to leave treatment decisions within the hands of the treating oncologists. All treatments, on-label or off-label remain fully reimbursed. Anticancer drugs available in another EU country or EMA, but not registered for pricing in Luxembourg can be obtained through an individualised compassionate use request addressed to the Ministry of Health.

Switzerland

People working in Switzerland and/or with permanent residency in the country are obliged to have a contract with one of many active health insurance providers. Although there is a minimum compulsory coverage, the whole number of covered scenarios varies greatly, along with involved premiums.[21] When it comes to a new EMA-approved treatment option, Swiss medic (swissmedic.

ch) provides an opinion/suggestion on overall benefit. If positive, the licence holder applies for authorisation and negotiates pricing with the Federal Office of Public Health (FOPH), leading to reimbursement by insurance providers. In case of absence of a positive FOPH decision (upcoming new indications or new clinical use without application to EMA for new indication), it is up to the treating physician to file a request to the insurance company that may approve or reject it, on assessment of evidence and benefit. In some cases, the health insurance provider comes to an agreement with the respective pharmaceutical company to split cost of treatment or switch reimbursement every second cycle. The treating physician may also ask the pharmaceutical company-licence holder to provide free-of-charge therapeutic for a fixed number of treatment cycles so that the potential benefit can then be individualised. If the patient indeed shows meaningful clinical benefit, the treating physician can reapply for coverage through the health insurance provider, though the latter has no obligation to cover the cost.

France

The French healthcare system allows a private and a public sector. Regarding pricing and reimbursement, the decision is made by a dedicated public agency.[22] For the practice of oncological treatment, hospitals, clinics or specialised centres must be accredited by the French National Cancer Institute (INCa) based on various criteria. Cancer diagnosis and care is covered at 100% by the Public Social Security through a mandatory contribution from all working and pensioned individuals at a cost agreed on by the French HTA bodyand applies to almost the entire population. Personal requests from a patient may be charged out of pocket. Once a diagnosis of cancer is made, the patient family physician or hospital file the case to the Social Security for the patient to be fully covered (retrospective diagnosis expenses will be retrospectively compensated).

Once a drug has been approved by the EMA, the MAH must apply to the French HTA body (ie, Haute Autorité de Santé in France) to start the process for pricing and reimbursement. This is a rather lengthy and complex process involving several agencies and commissions. As an average the mean duration for a drug from marketing authorisation to patient access is 530 days and a median of 405 days, all drugs considered. In order to facilitate accessibility to new drugs, compassionate use ('autorsiation temporaire d'utilisation', ATU) can be implemented. Drugs have to be used according to the EMA label and follow guidelines including the French Standards, Option and Recommendations form INCa, however, for older drugs, most often available as generics with a lower price, flexibility exists in practice, especially if the decision is approved by a multidisciplinary team, most often based on data generated in clinical trials post EMA approval.

Italy

To be marketed in Italy, a medicine must have obtained the marketing authorisation Autorizzazione all'Immissione in Commercio (AIC) from the (Agenzia Italiana del Farmaco (AIFA), even independently from the EC) or the European Commission. The AIC is issued following a scientific assessment of the quality, safety and efficacy requirements of the medicinal product.

According to the legislation there are four types of authorisation procedures: (1) national procedure, (2) mutual recognition procedure and decentralised procedure; (3) centralised procedure (it is coordinated by the EMA and is valid in all EU countries); (4) parallel importation (remark: this applies to all European countries). The AIFA constitutes the regulatory instrument that defines the therapeutic indications for which a given drug is reimbursable by the National Health Service ('Servizio sanitario nazionale',SSN).[23]

According to the law decree 648.96, the extension/update of indications related to uses of drugs is possible, based on scientific evidence present in the literature (indications different from those foreseen by the initial marketing authorisation). Therefore, extended indications for each drug are periodically updated and regulated by law (Italian specificity).

DISCUSSION

In the era of multidisciplinary, molecular oncology, the effort of research and development (R&D) of new cancer therapeutics is mostly taken up by the pharmaceutical industry. The associated cost is substantial and the whole R&D 'expenditure' needs to be driven by concrete incentives, in a large part financial. Consequently, the European legislation had delegated the task of applying for a new clinical indication to the MAH, which is usually a pharmaceutical company, along with commercial rights and a time period of exclusive manufacture and exploitation (patent).[24] After patent expiry, other pharmaceutical companies may produce generic versions of the therapeutic and on regulatory approval, become MAHs.

Scientific research by academia or other independent groups is becoming difficult in view of the financial, medicolegal and regulatory hurdles associated with it. Still, academia-led research is highly productive and results in hypothesis-generating promising data on optimisation of benefit and cost from existing therapeutics that warrant validation. Moreover, academic studies often generate robust, phase III trial data on new clinical uses and indications with meaningful benefit for the patient.[25 26] However, even in the presence of definitive phase III trial data that establish a new clinical use or indication for a cancer therapeutic, only its MAHs are by law entitled to apply to EMA for marketing authorisation on the new indication. An awkward No Man's land emerges, when the MAH has no intention (or incentive) to implement the latter. This is particularly true when the cancer therapeutics for which the new clinical indication

is established from phase III trials are off-patent drugs, available in several generic versions. Though seemingly trivial, the lack of official EMA marketing authorisation for the 'New' indication of an 'Old' anticancer drug results in either lack of, or operationally cumbersome and unpredictable, reimbursement and administration procedures in three out of five European countries that we sampled. This also reflects the different realities for patients 'access to evidence-based efficient treatment depending on national healthcare systems within the EU. The scenario of academia-led emerging evidence of lower cost, equally effective treatment regimens of expensive, innovative anticancer drugs, which is unlikely to be further clinically explored by the MAH for verification or rejection, raises questions at the heart of the prevailing driver principles of drug development: profit or health, both and at which priority?

Can we make progress and get more label extensions for evidence-based beneficial treatments? This is a scenario most commonly difficult in low-cost, off-patent generics or drugs close to an end of their initial patent, which have been shown to provide meaningful patient benefit in new clinical contexts. The new clinical use, when based on high-level evidence, should lead to an updated EMA approved indication. How can we get there?

The licence holder(s) will logically remain a central key player in the process to obtain a label extension. Thus, they have to be alerted and encouraged, maybe even supported in applying for a new indication. This implies dialogue between all stakeholders, including academia, oncological societies, patient advocacy groups, the pharmaceutical industry's licence holders and EMA. Non-profit stakeholders might (publicly) invite licence holders to move forward with a new EMA application. In this respect, it is encouraging that the European Commission is developing tools to encourage drug repurposing activities within the current legislative framework, in which drug repurposing will be driven by a 'champion' (any expert or academic entity or non-for-profit scientific society) in cooperation with the marketing authorisation holder.[27] Could this also apply to our setting? Could EMA's advice be asked in the prospect of a label extension by third parties so as to render the licence holder's application more promising?

National or supranational third payors should also be proactive in this area and be encouraged to proceed locally by financially supporting clinical studies in order to establish new indications. Such indications may benefit patients or optimise spending (eg, a label change leading to a shorter-duration treatment, etc). These payors could also reimburse nationally some indications even though they have not been approved on EU level.

Despite the undisputed success and positive impact of pharmaceutical R&D on availability of new cancer therapeutics and improved patient outcomes, we should acknowledge the need for a complementary, well-funded, non-for-profit R&D initiative.[28] There are scientific and clinical questions that pharma cannot or will not explore, questions that only such an independent research body can answer, to the benefit of our patients. Many questions, some promising leads. The authors of this paper believe that oncologists in academia or through professional societies should take initiative and actively work towards a solution—our patients deserve it!

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REFERENCES

1 European Medicines Agency. Authorisation of medicines, 2019. Available: https://www.ema.europa.eu/en/about-us/what-we-do/authorisation-medicines
2 European Medicines Agency. European Medicines Agency post-authorisation procedural advice for users of the centralised procedure, 2019. Available: https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/european-medicines-agency-post-authorisation-procedural-advice-users-centralised-procedure_en.pdf
3 European Commission. Guidelines on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of Commission regulation (EC) NO 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products and on the documentation to be submitted pursuant to those procedures: official Journal of the European Union, 2013. Available: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-2/c_2013_2008/c_2013_2008_pdf/c_2013_2804_en.pdf
4 Hidalgo M. Pancreatic cancer. *N Engl J Med* 2010;362:1605–17.
5 Conroy T, Hammel P, Hebbar M, *et al*. Folfirinox or gemcitabine as adjuvant therapy for pancreatic cancer. *N Engl J Med* 2018;379:2395–406.
6 ESMO Guidelines Committee. eUpdate – Cancer of the pancreas treatment recommendations, 2019. Available: https://www.esmo.org/Guidelines/Gastrointestinal-Cancers/Cancer-of-the-Pancreas/eUpdate-Cancer-of-the-Pancreas-Treatment-Recommendations
7 Zeghari-Squalli N, Raymond E, Cvitkovic E, *et al*. Cellular pharmacology of the combination of the DNA topoisomerase I inhibitor SN-38 and the diaminocyclohexane platinum derivative oxaliplatin. *Clin Cancer Res* 1999;5:1189–96.
8 United States Patent and Trademark Office. Patent terms extended under 35 USC §156, 2019. Available: https://www.uspto.gov/patent/laws-and-regulations/patent-term-extension/patent-terms-extended-under-35-usc-156
9 Neoptolemos JP, Palmer DH, Ghaneh P, *et al*. Comparison of adjuvant gemcitabine and capecitabine with gemcitabine monotherapy in patients with resected pancreatic cancer (ESPAC-4): a multicentre, open-label, randomised, phase 3 trial. *Lancet* 2017;389:1011–24.
10 Roche. Xeloda tablets SPC: European medicines Agency;, 2019. Available: https://www.ema.europa.eu/en/documents/product-information/xeloda-epar-product-information_en.pdf

11 Cunningham D, Allum WH, Stenning SP, *et al*. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N Engl J Med* 2006;355:11–20.
12 Al-Batran S-E, Homann N, Pauligk C, *et al*. Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): a randomised, phase 2/3 trial. *Lancet* 2019;393:1948–57.
13 ESMO Guidelines Committee. eUpdate: gastric cancer treatment recommendations, 2019. Available: https://www.esmo.org/Guidelines/Gastrointestinal-Cancers/Gastric-Cancer/eUpdate-Gastric-Cancer-Treatment-Recommendations
14 de Bono JS, Logothetis CJ, Molina A, *et al*. Abiraterone and increased survival in metastatic prostate cancer. *N Engl J Med* 2011;364:1995–2005.
15 Ryan CJ, Smith MR, de Bono JS, *et al*. Abiraterone in metastatic prostate cancer without previous chemotherapy. *N Engl J Med* 2013;368:138–48.
16 Fizazi K, Tran N, Fein L, *et al*. Abiraterone plus prednisone in metastatic, Castration-Sensitive prostate cancer. *N Engl J Med* 2017;377:352–60.
17 Chi KN, Spratlin J, Kollmannsberger C, *et al*. Food effects on abiraterone pharmacokinetics in healthy subjects and patients with metastatic castration-resistant prostate cancer. *J Clin Pharmacol* 2015;55:1406–14.
18 Szmulewitz RZ, Peer CJ, Ibraheem A, *et al*. Prospective international randomized phase II study of low-dose abiraterone with food versus standard dose abiraterone in castration-resistant prostate cancer. *J Clin Oncol* 2018;36:1389–95.
19 Storz U. Extending the market exclusivity of therapeutic antibodies through dosage patents. *MAbs* 2016;8:841–7.
20 Economou C, Kaitelidou D, Karanikolos M, *et al*. Greece: health system review. *Health Syst Transit* 2017;19:1–166.
21 De Pietro C, Camenzind P, Sturny I, *et al*. Switzerland: health system review. *Health Syst Transit* 2015;17:1–288.
22 Chevreul K, Berg Brigham K, Durand-Zaleski I, *et al*. France: health system review. *Health Syst Transit* 2015;17:1–218.
23 Mammarella F, Tafuri G. [Innovative medicinal products: the new criteria of the Italian Medicines Agency.]. *Recenti Prog Med* 2018;109:261–2.
24 Jones PS, Jones D. New regulatory framework for cancer drug development. *Drug Discov Today* 2012;17:227–31.
25 Protiére C, Baker R, Genre D, *et al*. Marketing authorization procedures for advanced cancer drugs: exploring the views of patients, oncologists, healthcare decision makers, and citizens in France. *Med Decis Making* 2017;37:555–66.
26 Jonsson B, Martinalbo J, Pignatti F. European medicines Agency perspective on oncology study design for marketing authorization and beyond. *Clin Pharmacol Ther* 2017;101:577–9.
27 Pharmaceutical Committee. Repurposing of medicines European Commission Expert Group on Safe and Timely Access to Medicines for Patients (STAMP), 2019. Available: https://ec.europa.eu/health/sites/health/files/files/committee/ev_20190711_co02_en.pdf
28 Hohl RJ. Drug development (and academic medicine): charting the course forward. *Clin Pharmacol Ther* 2014;96:519–22.