Patient access to new cancer drugs in the EU involves centralised licensing decisions by regulators as well as reimbursement recommendations in the context of national healthcare systems. Differences in assessment criteria and evidence requirements may result in divergent decisions at central and national levels, ultimately compromising effective access to patients. Early access decisions are particularly challenging due to the limited clinical evidence available to conclude on the benefit–risk and relative (cost-) effectiveness of new high-priced cancer drugs. We describe mechanisms to accelerate approval of promising anticancer drugs that fulfill an unmet medical need, review the experience from the European Medicines Agency, compare timelines and outcomes of reimbursement decisions in major EU markets, and discuss shortcomings of the current system, ongoing initiatives, and future steps to facilitate effective early access. **Key words:** conditional approval, accelerated approval, HTA, adaptive pathways, early access

### introduction

The European Medicines Agency (EMA) is responsible for providing a scientific opinion on the granting of EU-wide marketing authorisations for medicinal products, including new cancer drugs, for which the centralised evaluation procedure is mandatory [1]. The approval of new drugs in Europe is built on the benefit–risk (B/R) paradigm, based on objective criteria of quality, safety, and efficacy, and excludes any economic considerations. While often criticised for slowing down access to new therapeutic options for cancer patients with high unmet need, regulators have shown greater flexibility in the approval of cancer drugs than in other therapeutic areas, e.g. by not systematically requiring replication of pivotal trials and accepting preliminary evidence from promising albeit not validated surrogate end points and/or interim analyses, particularly in rare cancers.

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centralised regulatory early access tools

Regulatory agencies have long recognised the need to stimulate innovation and accelerate the development of cancer drugs in areas of high unmet need. To this aim, regulators can exercise considerable flexibility in determining the nature and level of evidence required for approval, when the potential therapeutic benefit to patients justifies assuming a greater degree of uncertainty in the B/R assessment. Debates about early access to cancer drugs have often focused on the definition and fulfilment of unmet medical need, the value of durable tumour responses in single-arm trials and of other surrogate end points to reasonably predict patient benefit, and on justifications to deviate from the usual requirement for randomised, controlled trials (RCTs) for regulatory approval [12-16]. The single-arm study design has major methodological weaknesses, and overall response rate (ORR) supported by duration of response (DoR) is generally not a recommended end point for licensing. However, compelling evidence of clinically relevant improvements in durable responses in uncontrolled phase 1/2 trials of good quality has resulted in approval of cancer drugs in various clinical contexts of high unmet need (Figure 1), such as highly pre-treated refractory patients, who often represent small target populations. Comprehensive preclinical validation of biological hypotheses and the absence of significant safety issues provide further support. Still, many caveats remain, mainly the lack of correlation of ORR with overall survival (OS) in specific solid tumours, which also poses significant challenges for HTA. However, it is acknowledged that conducting RCTs in the era of precision/stratified medicine can face major feasibility constraints, arising from the very low prevalence of certain molecularly defined subgroups and ethical dilemmas for randomisation due to perceived loss of ‘equipoise’ [17, 18]. Early identification of ‘high activity, unmet need (and uncertainty)’ situations where RCTs might not be strictly necessary for market access is critical, in order to discuss evidence generation with key stakeholders and ensure the viability of developments with potential for major therapeutic impact in niche indications [12, 15]. Early access can also be based on preliminary results from phase 2 or 3 RCTs, either from planned interim analyses pending confirmation by long-term follow-up of the same study (e.g. final OS analysis) or evidence considered reasonably persuasive but requiring replication in a new, often larger, trial (Figure 2B).

Several early access instruments to expedite development and regulatory review have been in place for many years, both in the EU—conditional marketing authorisation (CMA) and authorisation under exceptional circumstances, accelerated assessment—and in the USA, including fast-track designation, accelerated approval (AA), priority review, and more recently breakthrough designation [19]. However, while some instruments are in principle comparable in terms of scope and qualifying criteria between jurisdictions, their actual use has been uneven, both in terms of frequency and concordance (Table 1). While the majority of new cancer drugs authorised by FDA in the last 2 years were based on AAs (Table 1), this is in stark contrast to the scarce use of CMA in <25% of new cancer drugs licensed in the EU between 2006 and 2014. Earlier FDA approvals for virtually every cancer drug in the last 2 years suggest that the increased use of expedited programmes can have a significant impact on shortening regulatory review times (and potentially filing milestones), but also highlight the need for a differentiation mechanism in the EU similar to the FDA’s breakthrough designation [20].

conditional marketing authorisation

Since 2006 CMA can be granted to drugs intended for orphan, seriously debilitating or life-threatening diseases, or public health emergencies, on the basis of less than comprehensive clinical evidence. All of the following legal requirements have to be met: (i) the B/R balance of the drug is positive, (ii) it is likely that comprehensive confirmatory clinical data will be provided in a reasonable timeframe, (iii) the unmet medical need will be fulfilled by a major therapeutic advantage if alternatives are available or a favourable B/R is established in settings without viable treatment options, and (iv) the potential benefit to public health of the drug’s immediate availability outweighs the potential risks associated with the greater level of uncertainty about its B/R [21, 22]. Compared with FDA’s AA, an important difference is that CMA can only be applied to initial marketing authorisations, whereas AA can be used for variations (efficacy supplements) to facilitate early access to extensions of the drug’s use to new therapeutic indications. CMA is subject to legal requirements to fulfil specific obligations to confirm the favourable B/R, by completing ongoing or conducting additional studies. There should be reasonable guarantees on the feasibility and likelihood of timely completion of the agreed post-authorisation commitments, and in case of infringement, financial penalties can be enforced. CMA is subject to yearly renewals until its...
conclude that CMA is frequently used as a rescue option when available evidence is not sufficiently persuasive for regular authorisation, but that it does not necessarily result in promising products entering the market earlier [29]. A further criticism concerns the claimed excessive tolerance about unmet need (which, for some, potentially and/or resistance may constitute a therapeutic added value), that the B/R remains positive on the basis of emerging evidence from post-authorisation studies and pharmacovigilance.

In a recent study including the first 11 conditional approvals in oncology 2006–2013, a modest non-significant positive impact of CMA on clinical development times was largely offset by longer regulatory review. Of note, only 2 were upfront requests by applicants, while most were proposed by EMA late in the advisory process, to complement unmet need (which, for some, potentially and/or resistance may constitute a therapeutic added value). Figure 1. Cancer drugs with conditional or exceptional circumstances authorisation in the EU. ALK, anaplastic lymphoma kinase; ALL, acute lymphocytic leukaemia; AML, acute myeloid leukaemia; APL, acute promyelocytic leukaemia; BCC, basal cell carcinoma; CLL, chronic lymphocytic leukaemia; CMA, conditional marketing authorisation; CML, chronic myeloid leukaemia; CRC, colorectal cancer; DFSP, dermatofibrosarcoma protuberans; DLBCL, diffuse large B-cell lymphoma; ExC, authorisation under exceptional circumstances; GIST, gastrointestinal stromal tumour; HER2, human epidermal growth factor receptor 2; HES/CEL, hypereosinophilic syndrome/chronic eosinophilic leukaemia; KRASwt, Kirsten rat sarcoma viral oncogene homologue, wildtype; MDS/MSP, myelodysplastic syndromes/myeloproliferative diseases; MCL, medullary thyroid cancer; NHL-FL, non-Hodgkin’s lymphoma-follicular; NSCLC, non-small-cell lung cancer; paed, paediatric; RCC, renal cell carcinoma; SCLC, systemic anaplastic large cell lymphoma; SEGA, subependymal giant cell astrocytoma; STS, soft-tissue sarcoma; SCCHN, squamous cell carcinoma of the head and neck; SEGA, subependymal giant cell astrocytoma; STS, soft-tissue sarcoma; CMAvar/ExCvar, variations to initial conditional/exceptional circumstances authorisation, respectively, before ‘switch’ to regular authorisations.

In the EU, where CMA use has been more limited (and not possible for indication extensions), all granted by 2010 have been converted into regular approvals and no penalties have been imposed due to compliance infringements, although delays have been reported in a minority of cancer drugs [29]. A further criticism concerns the claimed excessive tolerance about uncertainty regarding safety, particularly rare serious adverse events, although studies on the incidence of post-approval safety-related actions (e.g. new warnings in the label and communications to healthcare professionals) for cancer drugs with CMA/AA remain inconclusive [30–33]. On the other hand, it has been argued that the current paradigm to qualify for CMA is excessively restrictive, in particular as regards the definition and fulfilment of unmet need (which, for some, potentially exists in any oncology setting lacking curative options), and that every new mechanism of action targeting other pathways and/or resistance may constitute a therapeutic added value per se [34, 35].
authorisation under exceptional circumstances

The legal scope is limited to exceptional situations in serious or life-threatening indications where it is not considered feasible to gather comprehensive clinical evidence according to conventional regulatory standards, primarily due to the extreme rarity of the indication. It is subject to annual re-assessment of the B/R and to specific obligations and conditions throughout the lifecycle, but without necessarily envisaging conversion into regular approval. In the first decade of EU-centralised evaluation (1995–2005), around one in four oncology initial approvals were granted under exceptional circumstances, including e.g. bortezomib, docetaxel, and imatinib, irrespective of the need for further confirmatory data, and most were later converted into normal authorisations based on evidence in new lines of treatment or different tumour types. However, since CMA was introduced, its use has been relegated to very rare cases (Figure 1).

accelerated assessment

The scientific assessment of the marketing authorisation application by the multidisciplinary Committee for medicinal products for human use (CHMP) involves two independent evaluation teams from national drug regulatory agencies, complex interactions with other EMA committees and working parties, and in controversial cases an external scientific advisory group of clinical experts is consulted. A positive CHMP opinion, which in most cases takes up to 210 days (maximum active review time defined in the legislation, excluding ‘clock-stops’ for applicant’s responses), is followed by a 2- to 3-month decision-making process by the European Commission (EC), resulting in a EU-wide marketing authorisation. In contrast to the FDA review procedure, in the EU there is no established rolling submission mechanism, and opportunities for information exchange with applicants are essentially limited to two time points in the evaluation procedure: 4 months after start, and close to finalisation in case of outstanding issues. The active evaluation time can be shortened to 150 days if accelerated assessment is granted, reserved for drugs of major public health interest, in particular therapeutic innovations. Out of 23 cancer drug applications that requested it in 2006–2014, 12 were not accepted due to uncertain clinical relevance, and several were reverted to standard timetables due to emerging major objections or inspections during CHMP evaluation. In contrast, the frequent use of priority review for cancer drugs by FDA has been shown to shorten review times by an average of 6 months compared with other therapeutic areas [36]. Efficiency gains in EMA review time might follow from the recent revision of the accelerated assessment guideline [37], but other measures like increasing communication with applicants pre-/during review are probably needed.

early dialogue: scientific advice

While EMA is not responsible for clinical trial approval in the EU, it is intensely involved in the drug development process by drafting general and disease-specific guidance [2], and at the level of individual products through established platforms like voluntary scientific advice. Requesting advice at any stage of development allows sponsors to have non-binding discussions with EU regulators, which may also involve FDA or national HTA bodies in ‘parallel advice’ procedures. Starting dialogue early to prospectively plan with regulators the optimal development. Regarding fulfilment of unmet need in the specific indication and level of evidence for initial CMA, topics often discussed are the definition of relapsed/refractory populations with regard to the number and type of prior treatments and sensitivity to preceding lines, the clinical relevance of expected or
already available results to qualify as a major therapeutic advantage over available therapy (eventually constructing plausible scenarios considering emerging competitors in dynamic therapeutic landscapes), and the type of acceptable evidence such as ORR and DoR data from uncontrolled trials, surrogate end points like pathological complete response [38] and minimal residual disease [39], and interim analyses from RCTs [40]. With regard to confirmatory evidence for conversion into regular approval, commonly discussed approaches include either more confirmatory RCT, the majority planned to be initiated pre-authorisation. Other common topics included eligibility for CMA, validation of biomarker-driven enrichment, and safety database.

**market access at national level**

Following the EU-wide authorisation, there is large variability in terms of procedures, timelines, and criteria in the P&R decision-making processes in each individual country (Figure 3), which ultimately determine effective access to new cancer drugs within the national healthcare systems. While the use of HTA as an instrument to inform P&R and drug utilisation decisions has increased dramatically in the last decade, its impact is variable, and methodological frameworks are diverse between countries [41], often leading to discrepant reimbursement decisions, in particular between systems that decide on coverage based on cost-effectiveness versus those relying on relative effectiveness analysis to influence price (Table 2). There is often variability in mechanisms and outcomes even within a given country, since different P&R frameworks can co-exist for cancer drugs administered in the hospital and ambulatory (community) settings, and independent regional HTA bodies may adopt divergent recommendations for the same drug. In England, broad coverage by the National Health Service (NHS) does not start until a formal

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**Table 1. Review/approval times and use of early access tools in the USA and EU for recently approved cancer drugs**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>FDA</th>
<th>EMA</th>
<th>Review time (days)</th>
<th>Difference in dates FDA–EMA (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pomalidomide (Imnovid)</td>
<td>Multiple myeloma</td>
<td>FT</td>
<td>BTD</td>
<td>CMA</td>
<td>CMA/CHMP Review start Approval</td>
</tr>
<tr>
<td>T-DM1 (Kadcyla)</td>
<td>Breast HER2+</td>
<td>FT</td>
<td>BTD</td>
<td>CMA</td>
<td>CMA/CHMP Review start Approval</td>
</tr>
<tr>
<td>Radium 223 Cl₂ (Xofigo)</td>
<td>CRPC</td>
<td>FT</td>
<td>BTD</td>
<td>CMA</td>
<td>CMA/CHMP Review start Approval</td>
</tr>
<tr>
<td>Dabrafenib (Tafinlar)</td>
<td>Melanoma BRAFm</td>
<td>FT</td>
<td>BTD</td>
<td>CMA</td>
<td>CMA/CHMP Review start Approval</td>
</tr>
<tr>
<td>Trametinib (Mekinist)</td>
<td>Melanoma BRAFm</td>
<td>FT</td>
<td>BTD</td>
<td>CMA</td>
<td>CMA/CHMP Review start Approval</td>
</tr>
<tr>
<td>Afatinib (Giotrif)</td>
<td>NSCLC EGFRm</td>
<td>FT</td>
<td>BTD</td>
<td>CMA</td>
<td>CMA/CHMP Review start Approval</td>
</tr>
<tr>
<td>Obinutuzumab (Gazyvaro)</td>
<td>CLL CD20+</td>
<td>FT</td>
<td>BTD</td>
<td>CMA</td>
<td>CMA/CHMP Review start Approval</td>
</tr>
<tr>
<td>Ibrutinib (Imbruvica)</td>
<td>MCL, CLL</td>
<td>FT</td>
<td>BTD</td>
<td>CMA</td>
<td>CMA/CHMP Review start Approval</td>
</tr>
<tr>
<td>Ramucirumab (Cyramza)</td>
<td>Gastric</td>
<td>FT</td>
<td>BTD</td>
<td>CMA</td>
<td>CMA/CHMP Review start Approval</td>
</tr>
<tr>
<td>Ceritinib (Zykadia)</td>
<td>NSCLC ALK+</td>
<td>FT</td>
<td>BTD</td>
<td>CMA</td>
<td>CMA/CHMP Review start Approval</td>
</tr>
<tr>
<td>Belinostat (Beleodaq)</td>
<td>PTCL</td>
<td>FT</td>
<td>BTD</td>
<td>CMA</td>
<td>CMA/CHMP Review start Approval</td>
</tr>
<tr>
<td>Idelalisib (Zydelig)</td>
<td>CLL, FL</td>
<td>FT</td>
<td>BTD</td>
<td>CMA</td>
<td>CMA/CHMP Review start Approval</td>
</tr>
<tr>
<td>Pembrolizumab (Keytruda)</td>
<td>Melanoma</td>
<td>FT</td>
<td>BTD</td>
<td>CMA</td>
<td>CMA/CHMP Review start Approval</td>
</tr>
<tr>
<td>Blinatumomab (Blynco)</td>
<td>ALL Ph-</td>
<td>FT</td>
<td>BTD</td>
<td>CMA</td>
<td>CMA/CHMP Review start Approval</td>
</tr>
<tr>
<td>Olaparib (Lynparza)</td>
<td>Ovarian BRCA1/2m</td>
<td>FT</td>
<td>BTD</td>
<td>CMA</td>
<td>CMA/CHMP Review start Approval</td>
</tr>
<tr>
<td>Nivolumab (Opdivo)</td>
<td>Melanoma</td>
<td>FT</td>
<td>BTD</td>
<td>CMA</td>
<td>CMA/CHMP Review start Approval</td>
</tr>
</tbody>
</table>

Median (days) 69% 44% 81% 56% 7% 7%

<table>
<thead>
<tr>
<th>n/total (%)</th>
<th>Median (days) 69% 44% 81% 56% 7% 7%</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA</td>
<td>EMA</td>
</tr>
<tr>
<td>200</td>
<td>333</td>
</tr>
<tr>
<td>49</td>
<td>210</td>
</tr>
</tbody>
</table>

*Selection of products includes first regulatory approvals in 2013–2014 (all but one, by FDA) for cancer drugs, status as of 15 September 2015.

**CMA/AccAs and review/approval dates not known for applications under review in EU (n/a).**

**EMA/CHMP ‘Review time’ includes clock-stops, but not European Commission decision timelines, which are, however, considered for the calculation of the difference in approval dates.**

**The difference in ‘Review start’ refers to dates of application submission to FDA and EMA, which only partially accounts for differences in approval dates.**

T-DM1, Trastuzumab emtansine; ALL, acute lymphocytic leukaemia; CLL, chronic lymphocytic leukaemia; CRPC, castrate-resistant prostate cancer; FL, follicular lymphoma; MCL, mantle-cell lymphoma; NSCLC, non-small-cell lung cancer; PTCL, peripheral T-cell lymphoma; FT, fast track; BTD, breakthrough designation; PRev, priority review; AA, accelerated approval; CMA, conditional marketing authorisation; AccAs, accelerated assessment; REV, initially accepted and later reverted to standard timetable; NO, request not accepted.
A recommendation has been issued by the National Institute for Health and Care Excellence (NICE), based on cost-effectiveness. In Germany, coverage by statutory health insurances starts right after regulatory approval, with free pricing in the first year, during which a decision from the ‘Gemeinsamer Bundesausschuss’ (G-BA) based on added therapeutic value follows, mainly impacting on the price. In France, the formal P&R decision involves a controlled pricing system informed by HTA, carried out by the ‘Haute Autorité de Santé’ (HAS) with a strong focus on added benefit, and bridging mechanisms are widely used for coverage of promising drugs, even before approval. In Italy, the ‘Agenzia Italiana del Farmaco’ (AIFA) has both regulatory and HTA/P&R competences. For medicines of exceptional therapeutic/societal benefit and orphan drugs, their P&R decisions should not exceed 100 days. To handle clinical/economic uncertainty, a national system of web-based registries closely monitors the use of new cancer drugs and collects outcome data to inform risk-sharing agreements. To foster collaboration between national and regional HTA organisations across Europe, EUnetHTA aims to promote more efficient use of resources, knowledge sharing, and methodology development, e.g. on rapid relative effectiveness assessment [42, 43].

**national early access mechanisms**

To provide cancer patients with high unmet need the opportunity to access new promising cancer drugs that are either not approved or have not been launched commercially yet, many EU countries have implemented early access programmes, which can at the same time provide very valuable evidence sources, complementary to clinical trials [44]. There are two main modalities, broadly based on the compassionate use framework, either in a predefined indication/population or as named-patient access on a case-by-case basis. Despite important differences in terms of evidence collection and transitional P&R conditions, the schemes overall share some common principles, such as restricting participation to patients with severe conditions and no available satisfactory alternatives nor possibility of enrolment into trials, and focusing coverage on pre-authorisation and/or on the period between approval and the national
<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>Pivotal clinical trial design (N)</th>
<th>Primary efficacy results (95% CI)</th>
<th>EU CMA</th>
<th>Outcome HTA/P&amp;R</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sunitinib (Sutent)</td>
<td>GIST 2L mono</td>
<td>Phase 3 RCT versus BSC (312)</td>
<td>PFS 6.25 versus 1.46 months—HR 0.33 (0.23–0.47)</td>
<td>July 06&lt;sup&gt;e&lt;/sup&gt;</td>
<td>R R I I R 32 n/a 2 4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ORR 25.5% (17.5%–34.9%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>RCC 2L mono</td>
<td>Phase 3 RCT versus BSC (463)</td>
<td>PFS 8 versus 7.3 months—HR 0.54 (0.443–0.663)</td>
<td>June 08&lt;sup&gt;e&lt;/sup&gt;</td>
<td>Susp. R III R n/a n/a 1 11</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ORR 25.5% (17.5%–34.9%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Panitumumab (Vectibix)</td>
<td>CRC KRASwt 2L+ mono</td>
<td>Phase 3 RCT versus BSC (154)</td>
<td>PFS 6.23 versus 4.26 months—HR 0.57 (0.43–0.77)</td>
<td>April 10&lt;sup&gt;e&lt;/sup&gt;</td>
<td>NO R V R 6 n/a 6 13</td>
</tr>
<tr>
<td>Lapatinib (Tyverb)</td>
<td>Breast HER2+ 2L comb. chemo</td>
<td>Phase 3 RCT add on to capecitabine (399)</td>
<td>PFS 6.23 versus 4.26 months—HR 0.57 (0.43–0.77)</td>
<td>September 11</td>
<td>n/a R II n/a n/a 4 n/a</td>
</tr>
<tr>
<td>Ofatumumab (Arzerra)</td>
<td>CLL 3L mono</td>
<td>Phase 2 single-arm (154)</td>
<td>ORR 58% (40%–74%)</td>
<td>June 10&lt;sup&gt;e&lt;/sup&gt;</td>
<td>R R NO R 8 n/a 8 11</td>
</tr>
<tr>
<td>Pazopanib (Votrient)</td>
<td>RCC 1L mono</td>
<td>Phase 3 RCT versus BSC (435)</td>
<td>PFS 9.2 versus 4.2 months—HR 0.46 (0.34–0.62)</td>
<td>September 11</td>
<td>n/a R II n/a n/a 4 n/a</td>
</tr>
<tr>
<td>Everolimus (Votubia)</td>
<td>SEGA paediatric 1L mono</td>
<td>Phase 2 single-arm (28)</td>
<td>volume 0.93 versus 1.7 cm&lt;sup&gt;3&lt;/sup&gt; (0.4–1.2)</td>
<td>September 11</td>
<td>n/a R II n/a n/a 4 n/a</td>
</tr>
<tr>
<td>Vandetanib (Caprelsa)</td>
<td>Thyroid, MTC 1L mono</td>
<td>Phase 3 RCT versus BSC (331)</td>
<td>PFS 30.5 versus 19.3 months—HR 0.46 (0.31–0.69)</td>
<td>February 12</td>
<td>n/a 3 IV R n/a 7 4 16</td>
</tr>
<tr>
<td>Poxantrone (Pixuvri)</td>
<td>DLBCL 2L mono</td>
<td>Phase 3 RCT versus BSC (140)</td>
<td>CR 20 versus 5.7% (3.5–25.1); P = 0.021</td>
<td>May 12</td>
<td>R 5 n/a NO 22 12 n/a 14&lt;sup&gt;NO&lt;/sup&gt;</td>
</tr>
<tr>
<td>Crizotinib (Xalkori)</td>
<td>NSCLC ALK+ 2L mono</td>
<td>Phase 1 single-arm + phase 3 RCT versus chem (125, 318)</td>
<td>phase 1 ORR 60%, phase 3 PFS 7.7 versus 3 months—HR 0.49 (0.37–0.64)</td>
<td>October 12</td>
<td>NO 2/5&lt;sup&gt;f&lt;/sup&gt; III R 10 6 17 29/5&lt;sup&gt;o&lt;/sup&gt;</td>
</tr>
<tr>
<td>Brentuximab vedotin</td>
<td>sALCL CD30+ 2L mono</td>
<td>Phase 2 single-arm (58)</td>
<td>ORR 75%, CR 33%, DoR 6.7 months</td>
<td>October 12</td>
<td>n/a 4 III R n/a 7 4 20/0&lt;sup&gt;o&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Hodgkin CD30+ 3L mono</td>
<td>Phase 2 single-arm (102)</td>
<td>ORR 75%, CR 33%, DoR 6.7 months</td>
<td>October 12</td>
<td>n/a 4 III R Exp 44 7 4 20/0&lt;sup&gt;o&lt;/sup&gt;</td>
</tr>
<tr>
<td>Bosutinib (Bosulif)</td>
<td>CML Ph+ 2L+ mono</td>
<td>Phase 2 single-arm (four cohorts: 502)</td>
<td></td>
<td>March 13</td>
<td>NO 4 V R 7 7 11 18</td>
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<tr>
<td>Vismodegib (Ervinege)</td>
<td>Basal cell, met. 1L mono</td>
<td>Phase 2 single-arm (two cohorts: 104)</td>
<td></td>
<td>July 13</td>
<td>n/a 3/5 IV R n/a 7 5 20</td>
</tr>
<tr>
<td>Cabozantinib (Cometriq)</td>
<td>Thyroid, MTC 1L mono</td>
<td>Phase 3 RCT versus BSC 2.1 (330)</td>
<td>PFS 11.2 versus 4 months—HR 0.28 (0.19–0.4)</td>
<td>March 14</td>
<td>n/a 3 IV n/a n/a 10 8 n/a</td>
</tr>
</tbody>
</table>

<sup>a</sup>England and Wales—NICE recommendation (impact on reimbursement); NO = not recommended; R = recommended; susp. = suspended; n/a = not appraised.
<sup>b</sup>Germany—additional benefit rating category: 1 = considerable; 2 = significant; 3 = small; 4 = not quantifiable; 5 = not demonstrated; 6 = inferior to available therapy;
<sup>c</sup>France—therapeutic value improvement: I = major, II = important, III = moderate, IV = minor, V = absent (impact on P&R). Times refer to HTA recommendations, which usually precede formal P&R decision by few weeks–months.
<sup>d</sup>Italy—NO = not reimbursed; R = reimbursed for hospital use.
<sup>e</sup>Reimbursement under Law 648/96 before formal P&R decision.
<sup>f</sup>different subpopulations/lines (since 2011 impact on price).

For abbreviations of therapeutic indications, please refer to Figure 1. BSC, best supportive care; CMA, conditional marketing authorisation; 95% CI 95% confidence interval; CR, complete response; DoR, duration of response; HR, hazard ratio; L, line of treatment; MCyR, major cytogenetic response; ORR, overall response rate; PFS, progression-free survival; P&R, price and reimbursement; RCT, randomised, controlled trial; superscript ‘S’, ‘switched’ to normal authorisation. Status as of 15 September 2015.
P&R decision. EU Member States may request a CHMP opinion on conditions for compassionate use, but there are no examples in oncology [45]. The French ‘Temporary Authorisation for Use’ (ATU) scheme has managed over 130 cohorts since 1994, with 19 currently ongoing covering more than 6000 patients in 2013. On average, the cohort ATU scheme provides effective access 1 year before centralised authorisation, and requires evidence generation which can later inform HTA by providing data relevant to the national context. Both prescription and supply are restricted to hospitals, who directly negotiate the initial ‘free pricing’ conditions with the pharmaceutical manufacturer, and full reimbursement is provided by the national healthcare system during the transition phase until the actual HTA-based P&R decision. Potential risks include interference with and delays of formal P&R decisions, and strategic use for seeding [46, 47]. The recently launched UK Early Access to Medicines Scheme (EAMS) aims to give access to medicines not yet authorised to patients with life-threatening or seriously debilitating conditions and clear unmet need. The Medicines and Healthcare products Regulatory Agency (MHRA) gives a scientific opinion on the B/R of the drug, which is provided by the manufacturer free of charge until EU authorisation. In Italy, while the final P&R decision is pending, AIFA can allow reimbursement of drugs for diseases with unmet need (Law 648/96), requiring data collection to inform HTA. For life-threatening diseases, free-of-charge access can be requested to manufacturers, under AIFA supervision, even to unapproved agents based on available phase 2 evidence (Decree 8/5/2003). In Germany, the ‘hardship case programme’ (‘Arzneimittel- Härtefall-Verordnung, AMHV’) allows distribution of yet unauthorised drugs, with case-by-case reimbursement negotiations.

emerging initiatives

EMA-HTA parallel advice consultation

P&R decisions at the national level are increasingly informed by HTA bodies, which operate under different methodological and legal frameworks, giving differential weight to criteria such as cost-effectiveness (NICE) or added therapeutic value (HAS, G-BA), and often resulting in divergent outcomes that ultimately give rise to disparities in access (Table 2). To deal with the increased complexity of market access of cancer drugs in the EU, recent initiatives have focused on early dialogue between pharmaceutical sponsors and regulators, HTA bodies, and P&R decision makers in order to ‘bridge the gap’ between their respective evidence requirements [5].

The joint EMA-HTA scientific advice procedure offers the opportunity to discuss key aspects of the clinical development of specific drugs with regulators and HTA bodies. The experience with >15 cancer drugs since start of the pilot in 2010 has highlighted the challenges in achieving agreement regarding key issues such as the choice of relevant comparators and end points, in some jurisdictions influenced by normative frameworks, and price/value discussions have been rather been an exception. At the same time, it has revealed the critical importance of considering the broad diversity of national preferences at the design stage in order to increase the chances of satisfying evidence requirements for HTA/P&R. The SEED (‘Shaping European Early Dialogues’ for health technologies) consortium is another pilot project, set up by the EC as a platform for early dialogue with a broader group of HTA bodies and EMA.

adaptive pathways

Newly emerging paradigms in early access include adaptive pathways (formerly adaptive licensing) which, as alternative to the current regulatory model based on binary licensing decisions, propose a prospectively planned systems approach to the entire lifecycle of the drug (development, licensing, reimbursement, and real-life use). Monitoring the dynamic evolution of the knowledge about the drug’s B/R, gained through iterative phases of evidence collection (including ‘real-world data’ outside the frame of RCTs) followed by its regulatory assessment, would lead to gradual adaptation of its license, in terms of authorisation status and extension or restriction of indications.

While based on available regulatory tools and processes (parallel scientific advice, CMA subject to conditions, risk management plans, observational studies, and post-approval safety/efficacy studies) within the current EU legal framework, adaptive pathways propose several innovative solutions, including efficacy-to-effectiveness studies, simulation methodologies, prescription controls to mitigate off-label use in the initial market access phases, and an increased emphasis on post-authorisation real-world evidence, which requires substantial capacity building for collection and analysis. Also, data-sharing platforms like the Project Data Sphere initiative can constitute very valuable sources of evidence [48]. Multi-stakeholder EMA-HTA scientific advice involving patients, healthcare professionals, HTA bodies, payers, regulators, and pharmaceutical companies from the initial development stages could facilitate alignment between evidence requirements of the various market access decision makers and prescribers/patients and promote synergies between regulatory instruments, national early access schemes, and innovative managed-entry coverage strategies, such as risk-sharing agreements to facilitate a graded, tightly managed, but more timely market entry [49, 50]. The pilot project started by EMA in 2014 has received 20 (33%) submissions for cancer drugs in its first year. Upon candidate selection on the basis of well-defined adaptation/iteration plans including real-world evidence rather than on unmet need or potential therapeutic breakthroughs, a handful of anticancer drugs have advanced into multilateral dialogue, but ongoing experience is yet too limited for a preliminary assessment.

conclusions and possible ways forward

Quantifying the actual impact of regulatory instruments on early market access for cancer drugs is complex, as it depends on several factors other than regulatory evidence expectations and review times [51]. Analyses in the past decade, before introduction of the breakthrough designation, did not observe significant differences in clinical development times between cancer drugs obtaining regular or accelerated FDA approval [32, 52]. In the European context, a very modest non-significant positive impact of CMA was largely offset by longer review times [23]. Ten years after the introduction of CMA, important questions about redefining the conditions for its optimal use are raised by the apparent heterogeneity in the clinical value of
drugs granted CMA. It has been speculated whether, in many cases, CMA use was motivated by the need to impose specific post-authorisation obligations to borderline approvable drugs rather than to expedite access to promising drugs [23]. Arguably, there have also been missed opportunities to expedite approval of several drugs of high value that obtained regular authorisation in the EU, with significant delays compared with their availability in the USA (Table 1). Furthermore, the acceptance of greater uncertainty by regulators is not necessarily shared by national HTA bodies (who in several cases deem the relative benefit of drugs with CMA as minimal, not quantifiable, or not demonstrated) and payers, which, added to the increasingly challenging P&R negotiations of high-priced cancer drugs, can result in delays of decisions or restrictions in effective access (Table 2). On the other hand, national early access mechanisms are sometimes used for drugs not yet approved or not selected for expedited review or CMA.

Therefore, early dialogue initiatives between regulators, HTAs, and P&R decision makers, but critically integrating clinicians’ and patients’ perspectives, are key in order to align evidence requirements and discuss perceptions of unmet need and added therapeutic value. This would ideally improve the selection of candidates for expedited access, optimise evidence generation, and foster effective early adoption. Recent initiatives from both ESMO [53] and ASCO [54] provide standardised approaches for grading the magnitude of clinical benefit which offer important insights, but place greater emphasis on relative effectiveness than on toxicity/risk and focus on RCTs. Further issues to address in the context of early access include the development of value criteria specifically focused on evidence from single-arm trials, value-based and sustainability-conscious approaches to pricing and implementation of risk-based coverage agreements. Other notable initiatives include the EC ‘Safe and Timely Access to Medicines for Patients’ (STAMP) group to explore hurdles and opportunities in the legislative-regulatory framework such as introducing CMA for indication extensions, Innovative Medicines Initiative (IMI) projects focused on the use of real-world data (GetReal) and adaptive pathways (ADAPTSMART), and collaborations between national HTAs (EUnetHTA) and competent authorities on P&R. Finally, there is clearly a need for greater support from regulators for the most promising candidate molecules likely to have a major therapeutic impact, in order to expedite both their development and approval. EMA is currently developing a scheme for priority medicines (PRIME), with prospective discussion of CMA, accelerated assessment, and multi-stakeholder early dialogue as main elements, to address the challenges of a rapidly evolving drug development landscape.

**note**

The views expressed in this article are the personal views of the authors and may not be understood or quoted as being made on behalf of or reflecting the position of the EMA or one of its committees or working parties.

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**references**


