European Conditional Marketing Authorization in a Rapidly Evolving Treatment Landscape: A Comprehensive Study of Anticancer Medicinal Products in 2006–2020

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Since 2006, the European conditional marketing authorization (CMA) aims to facilitate timely patient access to medicinal products for which there is an unmet medical need by accepting less comprehensive data than normally required. The granting of CMA requires a positive benefit–risk balance, unmet medical needs to be fulfilled, likely submission of comprehensive data postauthorization, and the benefit of immediate availability to outweigh the risks of data noncomprehensiveness. Since its first use, more than half of all CMAs represent (hemato-)oncology indications. Therefore, we aimed to investigate the conditions in which CMA has been applied for anticancer medicinal products and whether they have changed over time. We retrospectively assessed the European public assessment reports of the 30 anticancer medicinal products granted CMA in 2006–2020 (51% of all 59 CMAs). Comparison of 2006–2013 to 2014–2020 highlighted increased proportions of proactively requested CMAs (+40%), medicinal products that addressed unmet medical needs by providing a major therapeutic advantage over authorized treatments (+38%), and orphan designated indications (+32%). In contrast, it showed decreased proportions of medicinal products for which a scientific advisory group was consulted (−55%) and phase III randomized controlled trial data were available (−38%). This suggests that applicants and the European Medicines Agency have learned how to use the CMA as a regulatory tool, among others, through better planning and proactive interaction. However, the increasing number of granted CMAs complicates the establishment of unmet medical need and the benefit–risk balance, especially in crowded indications and when only phase II uncontrolled trials are available.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ Conditional marketing authorizations (CMAs) in Europe are mostly granted for anticancer medicinal products.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ In which conditions have CMAs been applied for anticancer medicinal products, and have they changed over time?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ Applicants and regulators seem to have learned how to use the CMA as a regulatory tool, among others, through better planning and proactive interaction. However, the increasing number of granted CMAs complicates the establishment of unmet medical need and the benefit–risk balance, especially in crowded indications and when only uncontrolled trials are available.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ Our findings highlight a need to critically consider how future decision making and legislation will ensure consistency and applicability of CMAs.

Worldwide, a medicinal product can only be authorized if it is of sufficient quality, has proven efficacy, and is relatively safe, such that its benefits outweigh its risks.[1] Since the establishment of the European Agency for the Evaluation of Medicinal Products (EMEA; now the European Medicines Agency or EMA) in 1995, two regulatory pathways have been available to establish a positive benefit–risk balance and authorize a new medicinal product throughout the European Union: standard marketing

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authorization (MA; sometimes called "full MA") and authorization under exceptional circumstances.[2–4] Standard MA requires robust and comprehensive safety and efficacy data to support the benefit–risk balance, together with the lowest possible level of scientific uncertainty. In contrast, authorization under exceptional circumstances recognizes situations in which obtaining comprehensive data may not be possible.[5]

A third regulatory pathway was added in 2006 to enable timely patient access to new medicinal products in therapeutic areas with an unmet medical need: the conditional marketing authorization (CMA).[6] Through this new "expedited" regulatory pathway, medicinal products for severely debilitating or life-threatening diseases, orphan diseases, or emergency situations can be authorized based on less comprehensive clinical data[6,7]—and potentially pharmaceutical and nonclinical data in emergency situations, such as the corona virus disease 2019 (COVID-19) pandemic.[6,8] Therefore, four prerequisites must be considered met by the EMA's Committee for Medicinal Products for Human Use (CHMP): (i) the available data indicate that the benefit–risk balance is positive, (ii) it is likely that comprehensive data will be provided postauthorization within a reasonable timeframe, (iii) unmet medical need will be fulfilled, and (iv) the benefit to public health of the medicinal product's immediate availability outweighs the risks associated with the uncertainty about its benefits and risks.[6,7] The potential to fulfill an unmet medical need can be established in settings without satisfactory authorized treatment options or when the medicinal product provides a major therapeutic advantage (MTA) over authorized treatments. Importantly, to ensure that comprehensive data will become available postauthorization, the holder of a CMA will need to complete "specific obligations"—often ongoing or new studies that must be performed and reported. A CMA is valid for 1 year only and must be renewed each year to ensure that the benefit–risk balance remains positive considering all available data, and to follow-up on the specific obligations.[6,7] Once comprehensive data have been obtained and confirm that the benefit–risk balance remains positive, a CMA will be converted into a standard MA, whereas, if not, the CMA may be revoked and the medicinal product withdrawn from the European market.[9] Of note, although the CMA shares similarities with the accelerated approval pathway in the United States, there are substantial differences between the two.[10]

CMAs have been granted for over 15 years. However, their characteristics and potential impact on drug development and regulatory decision making have not been investigated in-depth in more recent years. A previous report by the EMA, about the use of CMA for the first 10 years,[11] suggests that CMA may be seen as an important tool for fostering early access. Other studies have raised concerns that the use of CMA has become a rescue option when submitted data were not strong enough to support a standard MA, and that the possibility of CMA carries an inherent risk of lowering evidence standards.[12–15] To address these concerns, it is essential to assess how the prerequisites of CMA are met, and how its use has evolved since its establishment in 2006.

Reviewing the use of CMA is best done by focusing on a specific therapeutic area, especially one in which a great deal of drug development takes place. This allows an in-depth review of the characteristics of the regulatory process and the level of evidence associated with CMAs, as well as potential differences over time. Because the therapeutic area of oncology—including both solid tumors and hematological malignancies—is associated with high drug development activity and accounts for more than half of the CMAs,[4,11] it is ideally suited to assess this regulatory pathway. However, recent studies that addressed the impact of CMA on anticancer drug development and authorization are essentially lacking. Therefore, our aim was to investigate the conditions in which CMA has been applied for anticancer medicinal products and whether they have changed over time.

METHODS

Study design and cohort selection

We performed a retrospective cohort study that included all medicinal products assessed by the EMA and granted CMA in 2006–2020 for at least one (hemato-)oncology indication. These medicinal products were identified in the Union Register of medicinal products for human use[16] of the European Commission (EC). First, we identified all medicinal products authorized in 2006–2020. Second, we excluded medicinal products that had not been authorized based on a so-called "stand-alone application," also called "complete dossier" or "Article 8(3)" application. These excluded application types comprise generic ("Article 10(1)"), biosimilar ("Article 10(3)"), hybrid ("Article 10(4)"), and fixed-dose combination ("Article 10b") medicinal products, as well as medicinal products authorized based on the entire dossier of an already authorized medicinal product ("informed consent" or "Article 10c"), or based on literature because of "well-established use" ("Article 10a").[17] Third, we excluded those granted a standard MA or an MA under exceptional circumstances. Last, we excluded all medicinal products that had been granted CMA but were not authorized for at least one (hemato-)oncology indication.

Cohort characterization

For the included medicinal products, we collected basic characteristics, including the type of medicinal product (small molecule, biological, or advanced therapy medicinal product), the pharmacotherapeutic group according to their Anatomic Therapeutic Chemical (ATC) code, and the therapeutic area according to the initial indication(s). Initial indication(s) were extracted from the label at the time of authorization (i.e., the "Summary of Product Characteristics"), that is available in the EC Union Register. When a medicinal product had multiple (hemato-) oncology indications at initial authorization, these were all included, except for indications for which the supporting data were considered comprehensive and specific obligations were not required by the CHMP.

Data collection

For the included medicinal products and indications, we characterized the first three prerequisites of CMA: the evidence base that indicated that the benefit–risk balance was positive, the unmet medical need to be fulfilled, and the uncertainties stemming from noncomprehensive data that required specific obligations. The evidence base included the efficacy and safety database (i.e., the number of patients for whom data were available to establish efficacy and safety). We also characterized the use of regulatory procedures that may contribute to or be dependent on the evidence base, including regulatory support for clinical development (Priority Medicine (PRIME) status[18] and scientific advice), accelerated assessment, and whether the CMA was requested by the applicant. When submitting the regulatory dossier, applicants are required to apply for a specific regulatory pathway (i.e., standard, conditional, or exceptional MA). Furthermore, we characterized aspects that may indicate a more complex decision-making process by the CHMP, including consulting

of a Scientific Advisory Group (SAG), changes made to the indication requested by the applicant, and whether the CHMP opinion was formulated by consensus or majority vote. The data sources that were used to extract characteristics are listed in **Table S1**. We did not characterize the fourth prerequisite—the need for the benefit of immediate availability to public health to outweigh the risks associated with noncomprehensive data—because it is not extensively discussed in European public assessment reports. Data collection was performed by authors L.T.B. and J.S. Disagreement was resolved by discussion between authors L.T.B. and J.S. until consensus was reached.

Data categorization

We categorized several characteristics to allow summarizing them using descriptive statistics. First, we categorized indications by earliest line of treatment, meaning that it may also include later lines. The detailed indications are available in **Table S2**. Second, we categorized unmet medical need in two main categories: no satisfactory treatments authorized for that population or, if any, MTA over authorized treatments.[6,7] MTA was further described as pertaining to efficacy, safety, convenience, and/or other aspects (e.g., different pharmacodynamic profile).[7] Third, we compared the indication granted at CMA to the indication requested by the applicant and categorized changes as restriction, broadening, or specification of the indication. Minor differences that described specific population characteristics in pivotal trials were not considered changes to the requested indication. Fourth, we categorized uncertainties that required specific obligations in seven categories (i.e., concerning design of the pivotal trial(s), lack of long(er) term follow-up, limited database, specific subgroup(s), efficacy end points, specific safety issues, and/or other aspects). For the first four categories, we also defined whether these concerned the efficacy and/or safety of the medicinal product. Data categorization was performed by authors L.T.B. and J.S. and validated by authors L.L.-A. and O.T. (lines of treatment), authors C.H. and P.B.vH. (unmet medical need), or through discussion between all authors (changes to the requested indication and uncertainties). Disagreement was resolved by discussion between all authors until consensus was reached.

Identification of differences in CMA characteristics over time

Last, proportions of characteristics of regulatory procedures, the evidence base, and CHMP decision making were compared between the first 8 years of follow-up in our study (2006–2013) and the last 7 years (2014–2020) to identify potential differences over time.

RESULTS

Cohort characteristics: Medicinal products granted CMA and their initial indications

In the period 2006–2020, there were 1,139 medicinal products that were authorized by the EC after assessment by the EMA. Of these, 629 (55%) were authorized based on a stand-alone application ("Article 8(3)"). Of all medicinal products authorized based on a stand-alone application, 59 (9%) were granted a CMA; 30 for (hemato-)oncological indications that we included in our study, and 29 for other indications that we excluded. Among the excluded medicinal products were everolimus (Votubia), because it was indicated to treat a benign tumor, and genetically modified allogeneic T cells (Zalmoxis) because it was indicated as supportive treatment for hematological malignancies. **Figure 1** shows the proportion of these categories of medicinal products that were authorized during the study period, yearly, and overall. The 30 included medicinal products were conditionally authorized for 34 initial (hemato-)oncological indications. Of these 34 indications, 2 were not included in this study because the supporting data were considered comprehensive by the CHMP and thus no specific obligations were required: the gastrointestinal stromal tumor indication of sunitinib and the non-small cell lung cancer indication of entrectinib. **Table 1** provides aggregated characteristics of the 30 included medicinal products and the 32 indications, whereas **Table S2** provides a medicinal product-specific overview.

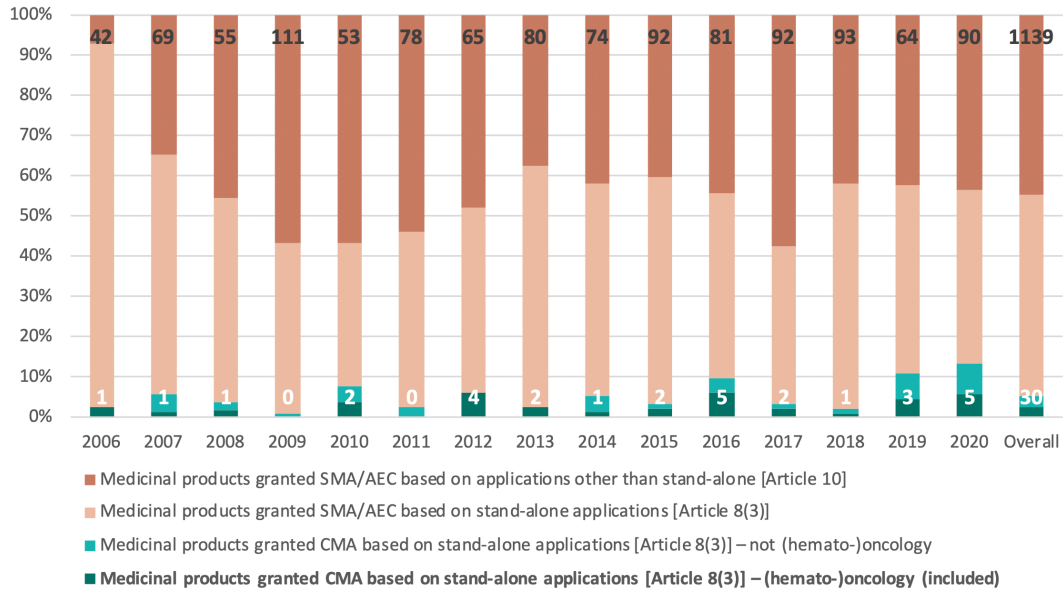

Figure 1 Proportion of medicinal products granted CMA with a (hemato-)oncological indication (2006–2020). The number of CMA medicinal products with a (hemato-)oncological indication that we included in the study is shown in white (yearly and overall). The total number of medicinal products authorized is shown in black. Please refer to the Methods section for an explanation of the type of applications. AEC, authorization under exceptional circumstances; CMA, conditional marketing authorization; SMA, standard marketing authorization.

Table 1 Characteristics of medicinal products granted CMA in 2006–2020 (*N* = 30) and their initial (hemato-)oncology indications (*N* = 32)

Characteristics		%
Type of medicinal product (*N* = 30 medicinal products)		
Small molecule	19	63
Biological	10	33
ATMP	1	3
Pharmacotherapeutic group[a] (*N* = 30 medicinal products)		
Cytotoxic antibiotics	1	3
Monoclonal antibodies and antibody drug conjugates	10	33
CD20 inhibitors	1	3
CD38 inhibitors	1	3
EGFR inhibitors	1	3
PD-1/PDL-1 inhibitors	2	7
Other monoclonal antibodies and antibody drug conjugates	5	17
Protein kinase inhibitors	14	47
ALK inhibitors	4	13
BCR-ABL tyrosine kinase inhibitors	1	3
EGFR tyrosine kinase inhibitors	1	3
HER2 tyrosine kinase inhibitors	1	3
Other protein kinase inhibitors	7	23
Other antineoplastic agents	5	17
Therapeutic area (*N* = 32 indications[b])		
Hemato-oncology	13	41
Leukemia, lymphoid	4	13
Leukemia, myeloid	1	3
Lymphoma, Hodgkin's disease	1	3
Lymphoma, non-Hodgkin's disease	4	13
Multiple myeloma	3	9
Solid tumors	19	59
Basal cell carcinoma	1	3
Breast cancer	1	3
Colorectal carcinoma	1	3
Cutaneous squamous cell carcinoma	1	3
Gastrointestinal stromal tumor	1	3
Medullary thyroid cancer	2	6
Merkel cell carcinoma	1	3
Non-small cell lung cancer	5	16
Ovarian, fallopian tube, or primary peritoneal cancer	1	3
Renal cell carcinoma	2	6
Soft tissue sarcoma	1	3
Tissue-agnostic	2	6

ALK, anaplastic lymphoma kinase; ATMP, advanced therapy medicinal product; BCR-ABL, breakpoint cluster region-Abelson; CD20/38, cluster of differentiation 20/38; CMA, conditional marketing authorization; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; PD-1/PDL-1, programmed cell death (ligand) 1.

[a]Based on Anatomic Therapeutic Chemical (ATC) code. [b]Four medicinal products were initially authorized with two indications (i.e., brentuximab vedotin, entrectinib, sunitinib, and venetoclax). For entrectinib and sunitinib, one indication was not included in this study because the data to support the indication were considered comprehensive and no specific obligations were required, see **Table S2**.

Table 2 Characteristics of the evidence base supporting the positive benefit–risk balance and the use of regulatory procedures (medicinal products ordered by date of authorization)

CMA		Indication			Use of regulatory procedures				Evidence base						
Active substance[a]	Year of CMA	Therapeutic area	Line[b]	Orphan	PRIME	Scientific advice	Applicant request for CMA	Accelerated assessment	Pivotal trial(s) phase	Pivotal trial design	Primary endpoint	Efficacy results	Phase 3 data available	Efficacy database	Safety database
Sunitinib	2006	RCC	2L	✗	N/A	✗	✗	✗	2	Uncontrolled	RR	36%; DoR: not reached	✗	106	450
Panitumumab[c]	2007	CRC	3L	✗	N/A	✗	✗	✗	3	Controlled (add-on to BSC)	TTP	Overall: 8.0 vs. 7.3 weeks, HR 0.60 (95% CI: 0.49–0.74); *KRAS* wild-type: 16.0 vs. 8.0 weeks, HR 0.49 (95% CI: 0.37–0.65)	Pivotal	243[d]	920
Lapatinib[c]	2008	Breast	3L	✗	N/A	✓	✗	✗	3	Controlled (add-on to capecitabine)	PFS	27.1 vs. 18.6 weeks, HR 0.57 (95% CI 0.43–0.77)	Pivotal	399	198
Ofatumumab[e]	2010	CLL	3L	✓	N/A	✗	✗	✗	2	Uncontrolled	RR	58%; DoR: 7.1 months[f]	✗	59	187
Pazopanib	2010	RCC	1L	✗	N/A	✓	✗	✗	3	Controlled (placebo)	PFS	9.2 vs. 4.2 months, HR 0.46 (95% CI 0.34–0.62)	Pivotal	435	586
Vandetanib[g]	2012	MTC	1L	✗	N/A	✓	✗	✗	3	Controlled (placebo)	PFS	30.5 vs. 19.3 months, HR 0.46 (95% CI 0.31–0.69)	Pivotal	331	231
Pixantrone	2012	NHL	3L	✗	N/A	✓	✓	✗	3	Controlled (physician's choice)	RR	20% vs. 6%; DoR: 9.6 vs. 4.0 months, HR 0.32 (95% CI 0.09–1.23)	Pivotal	140	407
Crizotinib	2012	NSCLC	2L	✗	N/A	✓	✓	✗	1/2	Uncontrolled	RR	60%; DoR: 48 weeks	Supportive	121	386
Brentuximab vedotin 1	2012	HL	3L	✓	N/A	✓	✗	✗	2	Uncontrolled	RR	75%; DoR: 6.7 months	✗	102	160
Brentuximab vedotin 2	Same medicinal product	sALCL	2L	✓	N/A	Same medicinal product	Same medicinal product	Same medicinal product	2	Uncontrolled	RR	86%; DoR: 13.2 months	✗	58	160
Bosutinib	2013	CML	2L	✓	N/A	✓	✗	✗	1/2	Uncontrolled	RR	CP: 9/36, AP: 3/5, BP: 2/11; CP DoR range: 8–204+ weeks[f,h]	Supportive	52	870

(Continued)

Table 2 (Continued)

CMA		Indication			Use of regulatory procedures				Evidence base						
Active substance[a]	Year of CMA	Therapeutic area	Line[b]	Orphan	PRIME	Scientific advice	Applicant request for CMA	Accelerated assessment	Pivotal trial(s) phase	Pivotal trial design	Primary endpoint	Efficacy results	Phase 3 data available	Efficacy database	Safety database
Vismodegib	2013	Basal cell	1L	✗	N/A	✓	✗	✗	2	Uncontrolled	RR	43% (met. 33%, l.a. 48%); DoR: 7.7 months (7.6, 9.5)	✗	96	138
Cabozantinib	2014	MTC	1L	✓	N/A	✗	✗	✗	3	Controlled (placebo)	PFS	48.6 vs. 17.4 weeks, HR 0.28 (95% CI 0.19–0.40)	Pivotal	330	295
Ceritinib	2015	NSCLC	2L	✗	N/A	✗	✗	✗	1	Uncontrolled	RR	56%; DoR: 8.3 months	✗	163	525
Blinatumomab	2015	ALL	2L	✓	N/A	✓	✓	✗	2	Uncontrolled	RR	43%; DoR: 6.7 months	✗	189	189
Osimertinib	2016	NSCLC	2L	✗	N/A	✗	✓	✓	2, 2 (pooled)	Uncontrolled	RR	66%; DoR: not reached	✗	398	411
Daratumumab	2016	MM	3L	✓	N/A	✓	✓	✓	2, 1/2	Uncontrolled	RR	29%, 36%; DoR: 7.4 months, not reached	✗	148	156
Olaratumab[l]	2016	STS	1L	✓	N/A	✓	✓	✓	1b/2	Controlled (add-on to doxorubicin)	PFS	6.6 vs. 4.1 months, HR 0.67 (95% CI 0.44–1.02)	✗	133	64
Ixazomib[c]	2016	MM	2L	✓	N/A	✓	✗	✗	3	Controlled (placebo, plus lenalidomide and dexamethasone)	PFS	20.6 vs. 14.7 months, HR 0.74 (95% CI 0.59–0.94)[f]	Pivotal	722	360
Venetoclax 1	2016	CLL	2L	✓	N/A	✓	✓	✗	2	Uncontrolled	RR	79%; DoR: not reached	✗	107	296
Venetoclax 2	2016	CLL	3L	✓	N/A	Same medicinal product	Same medicinal product	Same medicinal product	2[j]	Uncontrolled	RR	63%; DoR: not reached	✗	64	296
Alectinib	2017	NSCLC	2L	✗	N/A	✓	✗	✗	1/2, 1/2	Uncontrolled	RR	52%, 51% (pre-treated with chemotherapy: 45%); DoR: 14.9, 15.2 months	High-level interim analysis results	189	253
Avelumab	2017	MCC	1L	✓	✗	✓	✓	✗	2	Uncontrolled	RR	33% (2L+), 62% (1L); DoR: not reached[f]	✗	117	1,738
Rucaparib[k]	2018	Ovarian, fallopian tube, or primary peritoneal cancer	3L	✓	✗	✓	✓	✗	1/2, 2 (pooled)	Uncontrolled	RR	65%; DoR: 294 days	✗	79	409

(Continued)

Table 2 (Continued)

CMA		Indication			Use of regulatory procedures				Evidence base						
Active substance[a]	Year of CMA	Therapeutic area	Line[b]	Orphan	PRIME	Scientific advice	Applicant request for CMA	Accelerated assessment	Pivotal trial(s) phase	Pivotal trial design	Primary endpoint	Efficacy results	Phase 3 data available	Efficacy database	Safety database
Lorlatinib	2019	NSCLC	2L	✗	✗	✓	✓	✗	1/2	Uncontrolled	RR	43%, 39% (depending on extent of pre-treatment); DoR: 5.6, 9.9months	✗	139	295
Cemiplimab	2019	CSCC	1L	✗	✗	✓	✗	✗	2	Uncontrolled	RR	49% (met.), 44% (l.a.), 39% (met., different dose); DoR: not reached	✗	193	591
Larotrectinib	2019	Tissue agnostic	last-line	✗	✗	✗	✗	✗	1, 2, 1/2 (pooled)	Uncontrolled	RR	72%; DoR: not reached[f]	✗	102	125
Polatuzumab vedotin	2020	DLBCL	2L	✓	✓	✓	✗	✗	1b/2	Controlled (add-on to bendamustine and rituximab)	RR	40% vs. 18%; DoR: not assessed for primary endpoint	✗	80	45
Entrectinib	2020	Tissue agnostic	last-line	✗	✓	✓	✓	✗	2, 1, 1 (pooled)	Uncontrolled	RR	64%; DoR: 12.9months	✗	74	504
Belantamab mafodotin	2020	MM	5L	✓	✓	✓	✓	✓	2	Uncontrolled	RR	32%; DoR: 11.0months	✗	97	95
Avapritinib	2020	GIST	4L or 1L	✓	✗	✓	✓	✗	1	Uncontrolled	RR	95%; DoR: 22.1months	Supportive	38	585
Brexucabtagene autoleucel	2020	MCL	3L	✓	✓	✓	✗	✗	2	Uncontrolled	RR	85%; DoR: not reached	✗	74	82

ALL, acute lymphoblastic leukemia; AP, accelerated phase CML; BP, blast phase CML; BSC, best supportive care; CI, confidence interval; CLL, chronic lymphocytic leukemia; CMA, conditional marketing authorization; CML, chronic myelogenous leukemia; CP, chronic phase CML; CRC, colorectal carcinoma; CSCC, cutaneous squamous cell carcinoma; DLBCL, diffuse large B-cell lymphoma; DoR, duration of response (median); GIST, gastrointestinal stromal tumor; HL, Hodgkin lymphoma; HR, hazard ratio; l.a., locally advanced; MCC, Merkel cell carcinoma; MCL, mantle cell lymphoma; met, metastatic; MM, multiple myeloma; MTC, medullary thyroid cancer; N/A, not applicable (assessment started before PRIME existed); NHL, non-Hodgkin B-cell lymphoma; NSCLC, non-small cell lung cancer; PFS, progression-free survival (median); PRIME, Priority Medicine; RCC, renal cell carcinoma; RR, response rate; sALCL, systemic anaplastic large cell lymphoma; STS, soft tissue sarcoma; TTP, time to progression (median).
[a]Numbers indicate more than one initial indication, see also **Table S2**. [b]Indications can also include later-line treatment, see **Table S2** for precise wording of indications. [c]These medicinal products underwent a re-examination procedure following an initially negative CHMP opinion (panitumumab and ixazomib) or were re-assessed prior to the EC decision because concerns of hepatotoxicity were identified in ongoing clinical trials (lapatinib). [d]Number of patients for the post-hoc analysis in the *KRAS* wild-type subgroup. Initial primary analysis: 463 patients. [e]Marketing authorization withdrawn on February 25, 2019, for commercial reasons (after conversion to standard marketing authorization in 2015). [f]Results based on interim analyses of the primary end point. [g]Indication restricted to Rearranged during Transfection (RET) mutation positive medullary thyroid cancer on November 28, 2022, thereby facilitating conversion to a standard marketing authorization. [h]Population selected retrospectively as "unmet medical need" population. [i]Conditional marketing authorization revoked on July 19, 2019, because of negative confirmatory trial results. [j]Supportive instead of pivotal trial. The European public assessment report notes that the trial is "of major interest as the target population constitutes a population with unmet medical need." [k]Indication restricted to "maintenance indication" (added post-authorization) on September 21, 2022, because of negative confirmatory trial results for the initial CMA indication ("treatment indication").

Evidence bases supporting positive benefit–risk balance and use of regulatory procedures

Table 2 lists the evidence base that supported the positive benefit–risk balance for each indication but was not considered comprehensive. Over the entire period, phase I or II uncontrolled pivotal trials supported 23 of 32 indications (72%), whereas the response rate was the primary trial end point for 25 of 32 indications (78%) and at least some phase III randomized controlled trial (RCT) data were available for 11 of 32 indications (34%) at the time of CMA. Of these phase III RCTs, seven were pivotal trials on the basis of which the CMA was primarily granted, two—for crizotinib and alectinib—were ongoing and provided immature supportive data, and two—for bosutinib and avapritinib—missed their primary end points and were therefore considered supportive. All provided efficacy and safety data. The efficacy database comprised on median 119 patients (interquartile range (IQR) 80–190) and the safety database 296 patients (IQR 160–464) per indication. Additionally, Table 2 also highlights use of regulatory procedures such as orphan designation at time of CMA (17/32 indications, 53%), scientific advice (23/30 medicinal products, 77%), accelerated assessment (4/30 medicinal products, 13%), and whether the CMA was proactively requested by the applicant (13/30 medicinal products, 43%).

Established unmet medical need and other aspects of the CHMP decision-making process

Table 3 indicates how the CHMP expected medicinal products to address an unmet medical need in each indication. No satisfactory treatments were authorized for 19 of 32 indications (59%), whereas MTA over authorized treatments was established for 13 of 32 indications (41%). Furthermore, an SAG was consulted for 13 of 32 indications (41%), restrictions were applied to 13 of 32 indications (41%), and the CHMP decided about CMA by consensus vote for 21 of 32 indications (66%).

Uncertainties due to noncomprehensive data that required specific obligations

Table 4 lists the uncertainties that arose due to the lack of comprehensive data and that required specific obligations to obtain these data postauthorization. Most uncertainties were (at least) related to efficacy and the pivotal trial design (21/30 medicinal products, 70%) and sample size (16/30, 53%) were most often highlighted as causing uncertainties.

Differences in CMA characteristics over time

Figure 2 indicates differences in characteristics of conditionally authorized medicinal products between 2006–2013 and 2014–2020. The largest differences comprised increases in proactively requested CMAs (40 percentage points; 320% increase), unmet medical need defined as MTA over authorized treatments (38 points; 320% increase), and orphan designated indications (32 points; 200% increase), and decreases in the need to consult an SAG to inform CHMP decision making (55 points; 380% decrease), and availability of phase III RCT data at the time of CMA (38 points; 290% decrease). Table 4 also suggests an increase in the number of uncertainties with regard to the benefit–risk, but this may also be a consequence of the European public assessment reports having become more extensive and detailed in recent years.

DISCUSSION

We aimed to investigate the conditions in which CMA has been applied for anticancer medicinal products and whether they have changed over time. Typically, every regulatory assessment and decision about novel medicinal products carries inherent uncertainties.[19] However, well-informed decision making needs to be balanced by the provision of early access to promising treatments, particularly in the field of life-threatening diseases, such as cancer. Our study identifies European CMA as a relevant regulatory pathway to address this critical balance and oncology as its predominant clinical domain: during the study period, 9% of novel medicinal products were granted a CMA in the European Union, and half of them represented oncology and hemato-oncology indications. Recent studies have reported a similar trend in the United States concerning the use of accelerated approvals by the United States Food and Drug Administration,[20] highlighting that 28 of 30 accelerated approval decisions in 2020 represented (hemato-) oncology indications.[21]

Although increasing use of CMA and accelerated approval in (hemato-)oncology appears consistent over time and across regions, little cross-cutting information is known about the regulatory processes and the clinical evidence behind these decisions.[22] A key finding of our study is that the use of CMA appears to have changed from *ad hoc* use of CMA toward a more controlled use of the pathway by both regulators and companies, as evidenced by the increasing number of proactive requests for CMA by applicants (+40%), as well as fewer SAG consults (−55%) and more consensus decisions by the CHMP (+12%) when comparing 2006–2013 and 2014–2020. This may be explained by increased understanding of the types of data that may be acceptable for CMA and by the time needed to design drug development programs that take advantage of the pathway. Notably, the updated CMA guideline (2016) discussed in more detail which clinical data aspects could be acceptable for CMA and stressed the importance of prospective planning of both the pre-authorization and the postauthorization data package.[7] Furthermore, the early CMAs also show a higher proportion of ongoing phase III RCTs that were considered insufficient for a standard MA: their availability decreased with 38% in 2014–2020. This finding may be supportive of earlier critiques that CMA has initially been used as a rescue option more often than the intended prospectively planned early access pathway.[12,15] Alternatively, in more recent years, the type of medicinal products and their mutation-targeted (hemato-)oncology indications[23] may have prevented initiation of phase III studies due to, for example, the rarity of the disease.

Notably, the development of new anticancer medicinal products is not equally distributed across disease areas, and late-line settings of many specific disease entities have become more crowded than early treatment lines, as also indicated by our data, for example, for non-small cell lung cancer. This may be one of the underlying reasons for our finding that in recent years an increasing proportion of CMAs needed to show an MTA over authorized treatments

Table 3 Characteristics of established unmet medical need and other aspects of the CHMP decision-making process

Active substance[a]	Unmet medical need	SAG	Granted vs. requested indication	CHMP consensus vote
Sunitinib	No satisfactory treatment authorized	✓	Unchanged	✓
Panitumumab	No satisfactory treatment authorized	✓	Restricted to wild-type *KRAS*	✗[b]
Lapatinib	MTA: efficacy	✓	"Prior therapy" specified to include anthracyclines and taxanes	✗
Ofatumumab	No satisfactory treatment authorized	✓	Restricted to exclude fludarabine refractory, bulky lymphadenopathy CLL (for whom alemtuzumab is inappropriate)	✓
Pazopanib	MTA: different safety and pharmacodynamic profile	✓	2L+ specified to prior cytokine therapy	✗[b]
Vandetanib	No satisfactory treatment authorized	✓	Restricted to aggressive and symptomatic disease	✓
Pixantrone	No satisfactory treatment authorized	✗	Unchanged	✗
Crizotinib	No satisfactory treatment authorized	✗	Unchanged	✓
Brentuximab vedotin 1	No satisfactory treatment authorized	✓	Restricted to 3L, either after ASCT or when ASCT and multi-agent chemotherapy are not possible	✓
Brentuximab vedotin 2	No satisfactory treatment authorized	✓	Unchanged	✓
Bosutinib	No satisfactory treatment authorized	✗	Restricted to "unmet medical need population" who have exhausted or are unsuitable for imatinib, nilotinib and dasatinib; but including AP and BP Ph+CML	✓
Vismodegib	No satisfactory treatment authorized	✓	Metastatic BCC restricted to symptomatic; locally advanced BCC restricted to inappropriateness for radiotherapy, in addition to surgery	✗[b]
Cabozantinib	MTA: improved safety profile (no QTc prolongation)	✗	Unchanged	✓
Ceritinib	No satisfactory treatment authorized	✗	Previous treatment specified to crizotinib	✓
Blinatumomab	MTA: efficacy	✗	Unchanged	✓
Osimertinib	MTA: efficacy	✗	Unchanged	✓
Daratumumab	MTA: efficacy	✗	Unchanged	✓
Olaratumab	No satisfactory treatment authorized	✗	Unchanged	✓
Ixazomib	MTA: improved safety profile, convenience (oral)	✓	Unchanged[c]	✗
Venetoclax 1	No satisfactory treatment authorized	✗	Restricted to failure of or unsuitability for a B-cell receptor pathway inhibitor	✓
Venetoclax 2	No satisfactory treatment authorized	✗	Additional indication	✓
Alectinib	MTA: efficacy, also against CNS metastases	✗	Restricted to progression after crizotinib (not intolerant to)	✓
Avelumab	No satisfactory treatment authorized	✗	Unchanged	✗
Rucaparib	MTA: improved safety profile, convenience (oral)	✓	Restricted to relapsed or progressive disease (not maintenance treatment), unable to tolerate further platinum-based therapy; cancer types specified to epithelial ovarian, fallopian tube, and primary peritoneal	✗
Lorlatinib	MTA: efficacy, also against CNS metastases	✗	Unchanged	✗
Cemiplimab	No satisfactory treatment authorized	✗	Restricted to patients "who are not candidates for curative radiation", in addition to (curative) surgery	✓
Larotrectinib	No satisfactory treatment authorized	✓	Broadened to include primary CNS tumors and situations "where surgical resection is likely to result in severe morbidity"; treatment line specified as "no satisfactory treatment options"	✓

(Continued)

Table 3 (Continued)

Active substance[a]	Unmet medical need	SAG	Granted vs. requested indication	CHMP consensus vote
Polatuzumab vedotin	No satisfactory treatment authorized (2L); MTA (3L+): efficacy, improved safety profile, convenience (immediate availability vs. CAR-T)	✓	Unchanged	✗
Entrectinib	No satisfactory treatment authorized	✗	"Pediatric patients" restricted to 12 years and older; broadened to include situations "where surgical resection is likely to result in severe morbidity"; treatment line specified as "no satisfactory treatment options" and not after a prior NTRK inhibitor	✗
Belantamab mafodotin	MTA: efficacy, different safety profile	✗	Restricted to 5L+	✓
Avapritinib	No satisfactory treatment authorized	✗	Applicant withdrew 4L+ indication	✓
Brexucabtagene autoleucel	MTA: efficacy	✗	Restricted to 3L+ including prior therapy with a Bruton's tyrosine kinase inhibitor	✓

AP, accelerated phase; ASCT, autologous stem cell transplant; BCC, basal cell carcinoma; BP, blast phase; CAR-T, Chimeric antigen receptor T-cell; CHMP, Committee for Medicinal Products for Human Use; CLL, chronic lymphatic leukemia; CNS, central nervous system; KRAS, Kirsten rat sarcoma viral oncogene homolog; MTA, major therapeutic advantage; NTRK, neurotrophic tyrosine receptor kinase; Ph+CML, Philadelphia chromosome positive chronic myelogenous leukemia; SAG, Scientific Advisory Group.

[a]Numbers indicate more than one initial indication, see also **Table S2**. [b]Reasons for divergent opinions not published in the European public assessment report. [c]Modification of the indication to a subgroup as proposed by the applicant before the initial negative opinion was not considered acceptable by the CHMP. The re-examination again concerned the initially requested indication.

(+38%) instead of lacking authorized treatments altogether. Having more and more medicinal products available for patients and some therapeutic areas becoming relatively overloaded with medicinal products granted accelerated approval, has been considered valuable from a patient access perspective in the United States.[24] However, it may complicate the assessment of whether unmet medical needs are fulfilled. Although an MTA over other medicinal products can be based on more aspects than efficacy alone—including safety and "major improvements to patient care"[7]—it can become complex to establish based on noncomprehensive data, even if these data support a positive benefit–risk balance. This difficulty also becomes apparent from the divergent opinions expressed by CHMP members for the CMAs of rucaparib, lorlatinib, and polatuzumab vedotin.[25–27]

The changing use of CMA and the regulatory interpretation of MTA need to be considered in the context of change of the pivotal clinical datasets as, often along with uncertainties regarding efficacy, the results of our study indicate the pivotal trial designs and sample size as major sources of uncertainty and reasons for noncomprehensiveness of data. Our data indicate a trend in pivotal trials increasingly being uncontrolled, single-arm trials that are focused on demonstrating the antitumor activity of an anticancer medicinal product without interpretable information on time-related end points (overall or progression-free survival) or on their efficacy and safety as compared with standard of care. This observation is in line with previous studies that assessed the clinical data that support (hemato-)oncology CMAs and accelerated approvals,[28,29] and previous studies that showed an increasing trend in single-arm trial-based authorizations in the entire regulatory framework.[29–31] The data obtained in a single-arm trial may be sufficient to conclude that, based on the antitumor activity, there is most likely clinical benefit to patients, that the benefit–risk balance is positive, and that there is an MTA over authorized treatments. However, the extent of the benefit/MTA over other medicinal products cannot be assessed. Similar observations have recently been reported for the Canadian counterpart of CMA, the Notice of Compliance with Conditions (NOC/c).[32] Specific obligations that require (often randomized) postauthorization clinical studies should ultimately resolve these uncertainties and confirm the positive benefit–risk balance. However, many of the confirmatory trials for the conditionally authorized medicinal products in our study cohort are still ongoing. Future studies should update prior evaluations of how specific obligations are performed for CMAs,[33,34] and assess whether data from the confirmatory trials have provided the required comprehensive data and resolved key uncertainties (i.e., an important prerequisite of CMA). Notably, experience on revoking CMA due to failed specific obligations is currently very limited.[9]

A potential change in the impact of CMAs on patient access and downstream decision making by stakeholders, such as health technology assessment (HTA) organizations and clinical practice, remains to be established. However, the results of an earlier evaluation of CMAs granted in 2006–2016 suggest that CMA in general is associated with negative HTA outcomes.[35] Because our data indicate that rather fundamental uncertainties regarding both efficacy and safety have consistently been present in CMAs, it is reasonable to expect that the (hemato-)oncology CMAs based on single-arm trials and lacking data on time-related end points have had important consequences for subsequent decision making by HTA organizations on relative and cost-effectiveness, and ultimately on clinical

Table 4 Characteristics of uncertainties due to noncomprehensive data at time of CMA that required specific obligations (on medicinal product-level)

Active substance	Pivotal trial design[a]	Duration of follow-up	Sample size (database)	Subgroup[b]	Efficacy end point[c]	Specific safety issue	Other	Specific obligations (*N*)
Sunitinib			✗ S		✗			1
Panitumumab					✗[d]		✗[e]	14
Lapatinib					✗			2
Ofatumumab	✗ E	✗ E			✗			2
Pazopanib	✗ E&S							2
Vandetanib				✗ E				1
Pixantrone			✗ E[f]	✗ E				1
Crizotinib	✗ E&S	✗ E&S				✗		3
Brentuximab vedotin	✗ E&S	✗ E	✗ S	✗ E&S				4[g]
Bosutinib	✗ E		✗ E					1[g]
Vismodegib		✗ S	✗ E[f]&S	✗ E		✗		2[g]
Cabozantinib				✗ E			✗[h]	1
Ceritinib	✗ E							2
Blinatumomab	✗ E&S	✗ S						1
Osimertinib	✗ E[i]&S				✗			1
Daratumumab	✗ E		✗ S					2
Olaratumab	✗ E[j]		✗ E&S			✗	✗[k]	1
Ixazomib				✗ E	✗			4
Venetoclax	✗ E&S	✗ E	✗ E		✗			1[g]
Alectinib	✗ E&S							1
Avelumab	✗ E	✗ E	✗ E[f]	✗ E				1[g]
Rucaparib	✗ E[i]				✗			1
Lorlatinib	✗ E&S		✗ E	✗ E		✗		2
Cemiplimab	✗ E&S	✗ E&S	✗ E&S		✗		✗[l]	2[g]
Larotrectinib	✗ E	✗ S	✗ E	✗ E&S	✗	✗	✗[m]	3[g]
Polatuzumab vedotin		✗ E&S	✗ E&S	✗ E			✗[n]	2
Entrectinib	✗ E&S		✗ E&S[f]	✗ E&S		✗	✗[o]	2[g]
Belantamab mafodotin	✗ E&S		✗ S		✗		✗[p]	2
Avapritinib	✗ S	✗ E&S		✗ S		✗		3
Brexucabtagene autoleucel	✗ E	✗ E&S	✗ E	✗ E&S	✗	✗		2[g]

CMA, conditional marketing authorization; E, efficacy; S, safety.
[a]Mostly uncertainty due to uncontrolled pivotal trials. Alternatively due to, for example, pooled analyses. [b]Uncertainty about a subgroup with specific patient, disease or treatment characteristics, such as children, a mutation, or certain pretreatment. [c]Uncertainty about time-related end points, unless otherwise indicated. [d]Uncertainty about quality of life due to skin reactions. [e]Uncertainty about relationship between biomarkers—especially *KRAS* mutation status—and efficacy. [f]Uncertainty about limited efficacy or safety database in subgroup. [g]Trials required as specific obligation were solely (additional) uncontrolled trials. [h]Uncertainty about safety associated with a potential lower dosing regimen. [i]Uncertainty about trial design not explicitly mentioned, but clearly suggested because of uncertainty about quantification of time-related end points. [j]Only case where uncertainty about the trial design was expressed in context of a controlled pivotal trial—due to its early phase (1b/2, see **Table 2**). [k]Uncertainty about mechanism of action. [l]Uncertainty about relationship between biomarkers—especially PD-L1—and efficacy, and uncertainty about safety of commercialized dosing regimen. [m]Uncertainty about resistance mechanisms, the role of concomitant oncogenic drivers and recommended dose in pediatrics. [n]Uncertainty about heterogenous population and potential impact of anti-drug antibodies on efficacy. [o]Uncertainty about resistance mechanisms and the role of concomitant oncogenic drivers. [p]Uncertainty about safety of commercialized formulation and dosing regimen.
[Correction added on 17 May 2023, after first online publication: In Table 4, the formula mentioned in Pivotal trial design column for the active substance Avelumab has been corrected in this version.]

use.[36–38] This may be further complicated by the co-existence of multiple CMAs in specific disease entities and treatment lines. Moreover, studies required through specific obligations may not provide a solution for downstream decision makers.[39]

These observations bring to light the need for multistakeholder discussions between regulatory authorities, HTA organizations, industry, academia, clinicians, and patients, to evaluate the impact CMAs have had over time on drug development strategies,

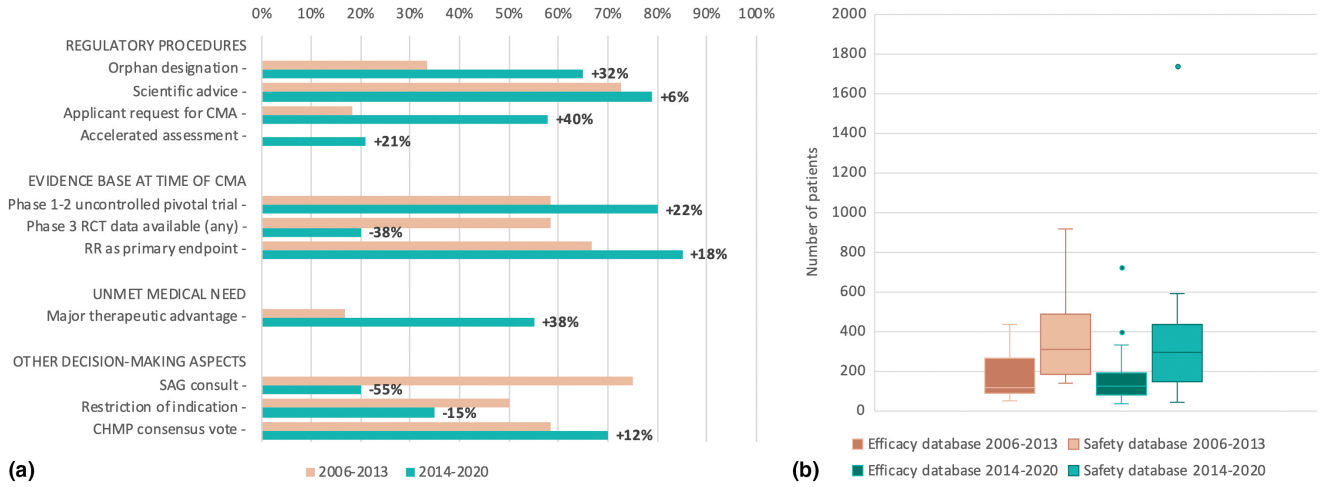

Figure 2 Characteristics of medicinal products granted CMA and their initial indications in 2006–2013 vs. 2014–2020. CMA, conditional marketing authorization; CHMP, Committee for Medicinal Products for Human Use; RCT, randomized controlled trial; RR, response rate; SAG, Scientific Advisory Group.

and whether and how this can be addressed in future legislation and decision making. Although use of CMA in earlier treatment lines might seem attractive, enabling larger patient groups to benefit from early access to promising therapeutic options would also increase the potential for harm due to adverse drug reactions and lack of efficacy in patients who may also have other treatments available. Furthermore, in such setting comparative efficacy and safety data, and thus an RCT, may be needed for demonstration of MTA, which would then require discussions on what type of data would be sufficient for CMA and when data can be considered sufficiently comprehensive for standard MA. Overall, regulatory and scientific efforts are thus needed to explore and advocate more optimal use of CMA while balancing the risks and benefits of early authorization.

This study provides the first comprehensive analysis of the evolution of the CMA, specifically for anticancer medicinal products. As such, it provides important insights and a basis for further discussion about its future use. However, it is difficult to generalize our findings to other CMA disease areas, such as infectious diseases or specific rare diseases. This requires one or more separate studies.

In conclusion, this study has identified changes in use of CMA in oncology and hemato-oncology through an analysis of authorizations between 2006 and 2020, and concurrent changes in clinical databases in support of them. Our findings indicate that both applicants and the EMA's CHMP have learned how to use the CMA as a regulatory tool, among others, through better planning and proactive interaction. At the same time, our data highlight a need to critically consider how future decision making and legislation will ensure consistency and applicability of CMA, particularly in terms of defining unmet medical need as MTA over authorized treatment options based on uncontrolled trials and enabling patient access.

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AUTHOR CONTRIBUTIONS

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DISCLAIMER

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 Dutch Medicines Evaluation Board, the Spanish Medicines Agency, the Finnish Medicines Agency, or the European Medicines Agency, or one of their committees or working parties.

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