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Review

European Union centralised procedure for marketing authorisation of oncology drugs: An in-depth review of its efficiency

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ABSTRACT

In the European Union (EU) 20 anticancer agents have been successfully authorised via the Centralised Procedure since its implementation in 1995. Public information on these 20 agents has been reviewed in order to evaluate the effectiveness of the available regulatory mechanisms to facilitate the marketing authorisation of such drugs in the EU. These mechanisms include orphan drug legislation, exceptional circumstances provision and the accelerated evaluation procedure. Based on the fact that the EU orphan drug legislation was not implemented before the year 2000 no conclusions on its effectiveness to facilitate oncology drug development can be drawn today. Much more data are available on the effects of the exceptional circumstances provision, which was used in 6 out of 10 cases over the past four years. An analysis of the clinical data packages indicates that this provision allows authorisation of innovative oncology drugs based on smaller clinical data sets than required for full approval. The accelerated evaluation procedure was used in only one case and significantly reduced the scientific review time at the EU agencies. However, this mechanism does not influence the administrative time at the authorities, which accounted for almost one-third of the overall duration of the EU marketing authorisation procedures for oncology drugs. Revision of the EU drug legislation brings about some changes to the above-described provisions, with the potential for an improvement in the current situation. Thus, its implementation offers the chance to reduce the time that innovative oncology agents take to reach the market, although – based on experience with the current procedures – more effort is likely to be required to achieve this goal.

1. Introduction

Oncology drugs can currently be authorised in the European Union (EU) via two different routes: the Mutual Recognition Procedure (MRP) can be used for all oncology drugs except biotechnological products, whereas the Centralised Procedure (CP) can be used for all innovative oncology drugs and has to be used for products manufactured by certain biotechnological processes.[1] However, due to revision of the EU drug legislation all new oncology drugs have to be authorised via the CP starting in November 2005 and will thus be reviewed by the Committee for Medicinal Products for Human Use (CHMP), formerly known as the Committee of Proprietary Medicinal Products (CPMP).[2]

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An in-depth review was performed evaluating the publicly available information on the marketing authorisation procedures for those oncology products that have been successfully authorised via the CP since its establishment in 1995. The main goal of this review was to evaluate the effectiveness of the available mechanisms to accelerate the marketing authorisation of oncology drugs in the EU. As clinical development is usually the time-limiting step for approval of innovative drugs, a thorough analysis of the clinical data packages for these products is also provided. Both analyses provide suggestions for future improvement of marketing authorisation procedures for new oncology agents.

There are currently three main mechanisms available in the EU that may be used to facilitate the development and the marketing authorisation process of oncology drugs: orphan drug legislation, exceptional circumstances provision and the accelerated evaluation procedure.

1.1. *Orphan drug legislation*

In the EU the orphan drug legislation was implemented in 2000.[3] Orphan drugs have access to the so-called 'Protocol Assistance' at the European Medicines Agency (EMEA), which usually requires lower fees than the EMEA Scientific Advice. Additionally, orphan drugs qualify more easily for the exceptional circumstances provision (see below). Thus, orphan drug status is considered to facilitate development of drugs for treatment of less frequent cancers, such as gliomas, renal cell cancer or certain haematological tumours.

An assessment of the usefulness of the orphan drug regulation cannot yet be made, as this regulation was not implemented in the EU before the year 2000.

1.2. *Exceptional circumstances provision*

The EU drug law, as currently codified in the *Commission Directive 2003/63/EC*,[4] allows that a marketing authorisation may be granted based on a reduced development programme (e.g. based only on phase II studies) under so-called 'exceptional circumstances'. These exceptional circumstances include development for use in a rare condition (e.g. orphan condition) or where in the present state of scientific knowledge, comprehensive information cannot be provided or when it would be unethical to collect further data. For anticancer agents the *CPMP Note for Guidance on Anticancer Medicinal Products*[5] further explains how to use these provisions in order to facilitate the development of oncology drugs. According to this guideline a marketing authorisation application can be based on data from uncontrolled clinical trials when there is no approved treatment available and an investigational drug shows outstanding anticancer activity. Additionally, this guideline endorses the use of tumour response as a surrogate endpoint, if it is justified to predict clinical benefit. Although this anticancer guideline provides no information for development of non-cytotoxic agents it has been used for the assessment of a number of such non-cytotoxic agents.

Overall, the exceptional circumstances provision has been used frequently over the past three years to facilitate the marketing authorisation of innovative oncology drugs in the EU.

1.3. *Accelerated evaluation procedure*

The EMEA first provided guidance[6] on an accelerated evaluation of products in 1996. This guidance foresaw a scientific review time of 120 d instead of the standard 210 d for drugs that meet the following three cumulative criteria:

- indicated for treatment of a heavily disabling or life-threatening disease and
- absence of an appropriate alternative therapeutic approach, and
- anticipation of exceptionally high therapeutic benefit.

Only one of the oncology drugs investigated has been authorised using an accelerated evaluation procedure.

2. Materials and methods

This review considered only new chemical or biological entities that belong to the Anatomical Therapeutic Chemical (ATC) Code categories 'L01 – Anti-neoplastic agents' and 'L02 – Endocrine therapy' and which the European Commission authorised for systemic anticancer treatment between January 1995 (start of the CP) and 30th June 2004. Other drugs used for treatment of patients with cancer, such as colony-stimulating factors, interferons and other immunomodulators as well as agents affecting bone structure and mineralisation (bisphosphonates), were not considered in order to ensure homogeneity of the investigated drugs and thus reduce variability of the results. A list of all products considered for analysis is given in Table 1.

Label extensions obtained after the initial marketing authorisations were not included in this analysis as they follow different procedures, so-called variations. Additionally, the impact of such label changes on the availability of new oncology drugs for patients is limited because the drug is already commercially available when a variation is submitted.

For all the products investigated, three different areas of information were evaluated:

1. Procedural information: this includes the orphan drug status, exceptional circumstances status and accelerated approval status. It was extracted from the European Public Assessment Reports (EPAR) which are published on the homepage of the EMEA.[7]
2. Timelines: timelines of the initial marketing authorisation procedure are defined for the purpose of this article as follows (see Fig. 1):
   - 'Active time' is the time needed for scientific evaluation by the CPMP as given in the Annual Reports of the EMEA. The Annual Reports of the EMEA can be retrieved from the EMEA homepage.[7]
   - 'Clock-stop time' is the time needed by the applicant to answer the objections raised by the authorities as given in the Annual Reports of the EMEA.
   - 'Scientific time' is the time needed for scientific evaluation by the CPMP plus the time needed by the applicant for answering the authority objections; it was calculated as the interval between the start of the

Table 1 – Evaluated oncology products sorted by date of first marketing authorisation (MA) in the European Union (EU) including procedural information

INN	Trade name	MA holder[a]	Date of first MA	Procedural information
Docetaxel	Taxotere	Rhone-Poulenc Rorer SA, France	27th November 1995	EC
Toremifene	Fareston	Orion Corporation, Finland	14th February 1996	N/A
Doxorubicin HCl	Caelyx	SP Europe, Belgium	21st June 1996	N/A
Topotecan	Hycamtin	SmithKline Beecham plc, UK	12th November 1996	N/A
Rituximab	MabThera	Hoffmann-LaRoche, UK	2nd June 1998	N/A
Temozolomide	Temodal	SP Europe, Belgium	20th January 1999	N/A
Tasonermin (TNF alpha)	Beromun	Boehringer Ingelheim International GmbH, Germany	13th April 1999	N/A
Paclitaxel	Paxene	Norton Healthcare Ltd., UK	19th July 1999	N/A
Doxorubicin HCl (liposome encapsulated)	Myocet	The Liposome Company, UK	13th July 2000	N/A
Trastuzumab	Herceptin	Roche, UK	28th August 2000	N/A
Capecitabine	Xeloda	Roche, UK	2nd February 2001	N/A
Bexarotene	Targretin	Ligand Pharmaceuticals UK Ltd., UK	29th March 2001	N/A
Alemtuzumab	MabCampath	Millenium and Ilex UK Ltd., UK	6th July 2001	EC
Temoporfin	Foscan	Scotia Pharmaceuticals Ltd., UK	24th October 2001	EC
Imatinib	Glivec	Novartis Europharm Ltd., UK	7th November 2001	EC, OD, AE
Arsenic trioxide	Trisenox	Cell Therapeutics, UK	5th March 2002	EC, OD
Ibritumomab	Zevalin	Schering AG, Germany	16th Jan 2004	EC
Fulvestrant	Faslodex	AstraZeneca UK Ltd., UK	10th March 2004	N/A
Bortezomib	Velcade	Millenium Pharmaceuticals Ltd., UK	26th April 2004	EC
Cetuximab	Erbitux	Merck KGaA, Germany	29th June 2004	N/A

INN, international non-proprietary name; EC, exceptional circumstances; OD, orphan drug; AE, accelerated evaluation; N/A, not applicable; MA, marketing authorisation.
a At time of procedure.

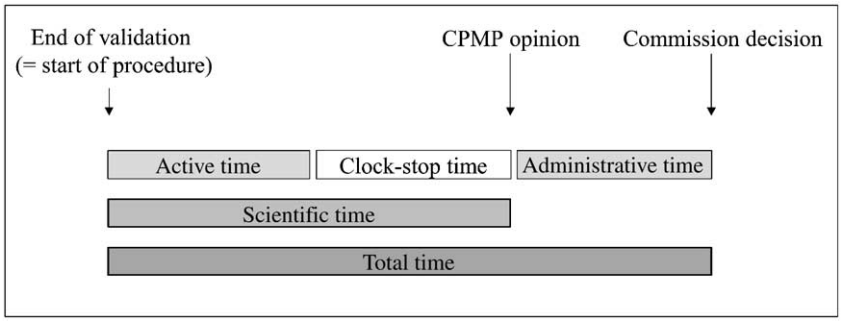

Fig. 1 – Overview on definitions of timelines. CPMP, Committee of Proprietary Medicinal Products.

procedure and the CPMP opinion as given in the Annual Reports of the EMEA, i.e. theoretically the sum of the active time and the clock-stop time; these times do not always sum up exactly to the total review times due to apparent different approximations used in the different sources. Where discrepancies across reports were noted, the time intervals were manually recalculated.

- 'Administrative time' is the time needed for translation and approval of the national product information, and publication of the Commission decision. Before the final Commission decision is released the draft Commission decision is also forwarded to a regulatory committee called the 'Standing Committee on Medicinal Products for Human Use' (Standing Committee) where representatives of the Member States have 30 d to raise objections. If important objections are raised, the CPMP is asked to formulate a reply, and a new Standing Committee procedure is started based on the CPMP answer. If the Standing Committee's opinion is favourable, the Commission will proceed with the decision-making process. According to current EU legislation the administrative time is foreseen to be 90 d.[8] The administrative time was calculated as the interval between the CPMP Opinion and the Date of Decision of the European Commission as given in the Annual Reports of the EMEA.
- 'Total time' is the time needed for the overall duration of the marketing authorisation procedure and was calculated as the interval between the start of the procedure and the Date of Decision of the European Commission as given in the Annual Reports of the EMEA, i.e. the sum of the scientific time and the administrative time.

- For products authorised in 2004 all data were taken and/or calculated from the EPAR, as the Annual Report 2004 was not yet available.
- Additionally, for each marketing authorisation procedure the proportion of the administrative time compared with the total time of the CP was calculated and given as a percentage value.

3. Clinical data: information on the clinical data packages, such as the size of the patient populations as well as the clinical data regarding study design and phase, primary endpoints, comparator(s) and numbers of patients, were extracted from the 'Scientific discussion' module of the EPARs as published on the homepage of the EMEA.[7]

The clinical data were used to investigate whether those marketing authorisation procedures performed under exceptional circumstances had reduced data requirements compared with those that were not performed under exceptional circumstances. For this purpose the data of three different parameters were classified as follows:

- Availability of phase III studies in the clinical development program.
- Size of the efficacy population: 250 patients or more versus less than 250.
- Size of the safety population: 500 patients or more versus less than 500 patients.

For the two groups of drugs, i.e. those authorised via exceptional circumstances versus those with a full marketing authorisation, the percentage of drugs falling into each class was calculated and the data were analysed descriptively.

3. Results

3.1. *Procedural information*

As outlined above, there are three main mechanisms available, which may be used to facilitate the development as well as the marketing authorisation process of oncology drugs in the EU: orphan drug legislation, exceptional circumstances provision and the accelerated evaluation procedure. For each of the 20 oncology drugs investigated, information is provided regarding these mechanisms in Table 1.

Two of the 20 oncology drugs investigated were granted orphan drug status before their marketing authorisation procedure started (Glivec and Trisenox).

In fact, 7 (35%) of the 20 oncology drugs investigated have been authorised under exceptional circumstances. Six out of 10 (60%) drugs authorised since the beginning of 2001 were authorised under these conditions. Based on additional clinical data submitted by the applicant, Taxotere has meanwhile received full approval. As the other drugs have only been authorised during the past three years they are still regarded as authorised under exceptional circumstances and have to fulfil post-marketing obligations in order to achieve full approval status.

Only 1 of the 20 drugs reviewed by the CPMP thus far, i.e. Glivec, was reviewed in an accelerated evaluation procedure. As a consequence, Glivec is the product that has the shortest total time for the EU marketing authorisation procedure (225 d) among all oncology drugs investigated (for details see below).

3.2. *Timelines of the initial marketing authorisation procedure*

3.2.1. *Total time*

The shortest total time of all oncology drugs investigated was observed for Glivec, at 225 d, whereas the longest total time was observed for Foscan, at 734 d. However, these 734 d included a so-called appeal procedure because the CPMP had initially issued a negative opinion on Foscan that was subsequently revised to become a positive opinion based – among other factors – on certain label changes. The mean as well as the median total time is in the range 13–14 months (429 and 418 d, respectively; see Table 2).

3.2.2. *Active time*

The active time for scientific evaluation of the marketing authorisation application by the authorities is below 210 d in 75% of cases, which is the target defined by EU legislation.[8] In 20% of cases it was slightly higher. In only 1 case the benchmark of 210 d was clearly missed (Fareston). An active time considerably below 150 d was only achieved in 2 cases: for Glivec, which had qualified for accelerated evaluation, and for Taxotere, where the short active time can be explained by the fact that the review had already started under the former concentration procedure in 1994, but only the review time under the CP starting on 1st January 1995 was calculated.

3.2.3. *Clock-stop time*

The mean clock-stop time was 119 d, with the majority of products having a clock-stop time of 3–9 months. By far the longest clock-stop time (305 d) was observed for Herceptin, because the applicant had to implement during this time a single-dose vial instead of the proposed multi-dose vial. The authorities had requested this change because benzylalcohol which was used as a conserving agent for the multi-dose vial is not allowed as a conserving agent for intravenous products in the EU.

3.2.4. *Scientific time*

On average, the scientific time was 312 d, ranging from 121 to 615 d. A scientific time of 615 d was needed for Foscan as an appeal procedure was required before the CPMP issued a positive opinion (see above).

3.2.5. *Administrative time*

The mean administrative time for the investigated oncology CPs was 117 d and ranged from 92 up to 173 d. Thus, in no case the administrative process was completed within the target time frame of 90 d. The maximum time of 173 d was observed for Paxene where the decision-making process was temporarily suspended.

Table 2 – Timelines

Trade name	Active time (d)	Clock stop (d)	Administrative time (d)	Scientific time (d)	Total time (d)	Administrative time of total time (%)
Taxotere	100[a]	93	138	192	330	42
Fareston	240[a]	50	120	289	409	29
Caelyx	222[a]	150	129	408	537	24
Hycamtin	154	28	116	185	301	39
Mabthera	179	132	125	313	438	29
Temodal	203	60	96	265	361	27
Beromun	188	204	145	391	536	27
Paxene	179	251	173	432	605	29
Myocet	167	91	92	257	349	26
Herceptin	147	305	95	454	549	17
Xeloda	201	159	106	364	470	23
Targretin	197	159	133	335	468	28
MabCampath	203	142	99	349	448	22
Foscan	215	238	119	615[b]	734	16
Glivec[c]	119	0	104	121	225	46
Trisenox	180	51	138	233	371	37
Zevalin	153	28	113	185	298	38
Faslodex[d]	212	57	111	269	380	29
Velcade[d]	175	155	96	331	427	22
Erbitux[d]	214	33	97	247	344	28
Mean	182	119	117	312	429	29
Median	184	113	115	301	418	28

a Procedure started as concentration procedure; thus start of CP was set arbitrarily on 1st January 1995.
b Including appeal procedure.
c Authorised via an accelerated evaluation procedure.
d Data taken and/or calculated from EPAR as Annual Report 2004 not yet available.

The ratio of the administrative time to the total time of the CPs ranged from 16% to 46%, with a mean of 29%. As the variability of the administrative time is fairly low the extreme values were observed for the shortest and the longest marketing authorisation procedure, i.e. Glivec as the shortest procedure had the highest value (46%) and Foscan had the lowest value (16%).

3.3. *Clinical data*

The majority of the clinical data packages consisted of 2–3 efficacy studies with a mean of 314 patients being treated with the investigational compound in these studies (Table 3). The mean safety population had approximately double that size, encompassing on average 632 patients in the target indication. Interestingly, 1 marketing authorisation was granted with as little as 52 patients in a single efficacy study (Trisenox). The largest development program was provided for Glivec with 1027 patients being treated in 3 large phase II studies.

Of note, in none of the development programs for initial marketing authorisation was survival used as the primary endpoint. Only for Fareston, in a meta-analysis for demonstration of non-inferiority, was survival one of multiple primary endpoints – besides response rate and time to progression. The most commonly used endpoint was response rate (14 out of 20 development programs, i.e. 70%). However, it has to be noted that different definitions of response rate were employed depending on the requirements of the target indication (for details see Table 4).

Four out of the 20 drugs investigated were authorised based on non-inferiority studies (Fareston, Myocet, Xeloda and Faslodex) and all four used active comparators. Of the 16 drugs that were authorised based on superiority approaches, only 5 (Caelyx, Hycamtin, Temodal, Herceptin and Zevalin) included active comparators in their efficacy studies. This indicates that most of the drugs investigated were developed in end-stage cancer settings where no other drugs were already authorised and thus no active comparators could be used.

For 9 out of the 20 compounds phase III studies were performed. These nine drugs include those using non-inferiority approaches and additionally Caelyx, Hycamtin, Mabthera, Herceptin and Zevalin. However, for MabThera one efficacy study was designated as a phase III study that did not include an active comparator but was historically controlled.

As indicated above, it was also investigated whether smaller clinical data packages were acceptable for marketing authorisations granted under exceptional circumstances compared with full marketing authorisations. This analysis demonstrates (see Fig. 2) that clinical development programs of drugs authorised via exceptional circumstances in more than 80% of the cases did not involve phase III studies and included less than 250 patients treated with the new drug in efficacy studies. In contrast, only approximately 40% of the development programs resulting in full approval had no phase III studies and approximately 20% had less than 250 patients treated with the new drug in efficacy studies. A similar trend was observed for the size of the safety population although it was not as pronounced. For 50% of the marketing

Table 3 – Overview of clinical packages

Trade name	Indication	Efficacy studies (*n*)	Efficacy population[a] (*n*)	Safety population[b] (*n*)
Full marketing authorisations				
Fareston	Hormone-dependent metastatic breast cancer (1st line)	3	592	N/A
Caelyx	AIDS-related Kaposi's sarcoma	3	517	825
Hycamtin/Evotopin	Advanced ovarian carcinoma	4	392	445
Mabthera	Follicular lymphoma	2	203	282
Temodal	Glioblastoma multiforme	2	250	993
Beromun	Soft tissue sarcoma of the limb	4	260	260
Paxene	AIDS-related Kaposi's sarcoma	1	107	543
Myocet	Metastatic breast cancer	3	330	720
Herceptin	Metastatic breast cancer	2	311	900
Xeloda	Metastatic colorectal cancer (1st line)	2	603	1024
Targretin	Cutaneous T-cell lymphoma (CTCL)	2	152	152
Faslodex	Locally advanced or metastatic breast cancer	2	428	1149
Erbitux	Metastatic colorectal cancer (2nd line)	1	329	522
	Mean	2.4	344	651
Marketing authorisations under exceptional circumstances				
Taxotere	Advanced breast cancer (2nd line)	3	111	N/A
MabCampath	Chronic lymphocytic leukaemia (CLL)	3	149	700
Foscan	Advanced head and neck cancer	1	147	855
Glivec	Chronic myeloid leukaemia (CML)	3	1027	1170
Trisenox	Acute promyelocytic leukaemia (APL)	2	52	251
Zevalin	Non-Hodgkin's lymphoma (NHL)	1	73	211
Velcade	Multiple myeloma (3rd line)	2	246	379
	Mean	2.1	258	594
All marketing authorisations	*Mean*	2.3	314	632

N/A, data not available.
a Intention-to-treat population.
b Population treated with study drug.

authorisations granted under exceptional circumstances a safety population of less than 500 patients in the target indication was required, whereas this was only sufficient in approximately 30% of the programs resulting in full approval.

4. Discussion

The duration of marketing authorisation procedures for innovative drugs – especially for those designed to treat life-threatening diseases such as cancer – is often a matter of debate.[9–11] However, the current legislative framework in the EU already offers mechanisms to accelerate the marketing authorisation of oncology drugs in the context of the CP. In order to provide objective information for future improvements in the EU regulatory system the effectiveness of these mechanisms was evaluated in a series of anticancer agents that have been authorised via the CP since its implementation in 1995 up to mid-2004. These mechanisms are not available for marketing authorisation of oncology drugs via the MRP. Thus, new oncology drugs authorised in the EU via the MRP have not been considered in this review.

One of these mechanisms for facilitation of oncology drug development is orphan drug legislation. Based on the fact that the new EU orphan drug legislation was implemented only in the year 2000, only two orphan drugs have been authorised as anticancer agents thus far. Therefore, no conclusions on the effectiveness of the orphan drug provisions with respect to facilitation of the marketing authorisation process of oncology drugs can be drawn. However, between August 2000 and the cut-off for this review on 30th June 2004 approximately 60 orphan drug designation applications for oncology indications were approved by the European Commission.[12] Thus, many investigational anticancer agents having an orphan drug status are currently in development. As a consequence, it is expected that much more experience in this area will soon be available.

Another mechanism for facilitation of development of oncology drugs is the exceptional circumstances provision. This mechanism has been used in approximately 40% of the investigated marketing authorisation procedures with an increasing trend over the last three years. This analysis also indicates that the exceptional circumstances provision really allows authorising innovative oncology drugs based on smaller clinical data packages. Thus, the exceptional circumstances provision represents a powerful tool to get new oncology drugs faster to patients in the EU.

With the new EU legislation[2] it will be possible in the future to grant a so-called 'conditional marketing authorisation'. A conditional marketing authorisation will be valid only for a period of one year and then will need to be reviewed again by the CHMP. The conditional approval will allow marketing authorisation of innovative drugs based on limited data even when there is a chance of generating a full data set. In contrast, the exceptional circumstances provision only

Table 4 – Overview of clinical data

Trade name	Study code	Study design	Phase	Primary endpoint	Patients on study drug (*n*)	Study drug result	Comparator	Patients on comparator (*n*)	Comparator result
Taxotere	Meta-analysis of 3 studies	Open, multicentre, non-comparative	2	Overall response rate	111	49%	N/A	N/A	N/A
Fareston	5/044	Open, multicentre, randomised	3	Response rate difference, time to progression hazard ratio, overall survival hazard ratio (all non-inferiority); meta-analysis	592	RR – 0.8% TTP 0.91 OS 1.00	Tamoxifen	565	N/A
Fareston	5/049	Double-blind, multicentre, randomised	3						
Fareston	5/050	Open, multicentre, randomised	3						
Caelyx	First study	Open, multicentre, non-comparative	2	Overall response rate	247	81%	N/A	N/A	N/A
Caelyx	Second study	Open, multicentre, non-comparative	2	Overall response rate	137	62%	N/A	N/A	N/A
Caelyx	Submitted during procedure	Open, multicentre, randomised	3	Overall response rate	133	46%	Adriamycin, bleomycin, vincristine[b]	125	26%
Hycamtin	039	Open, multicentre, randomised	3	Overall response rate	112	21%	Paclitaxel	114	14%
Hycamtin	034	Open, multicentre, non-comparative	2	Overall response rate	111	14%	N/A	N/A	N/A
Hycamtin	033	Open, multicentre, non-comparative	2	Overall response rate	139	15%	N/A	N/A	N/A
Hycamtin	012	Open, single centre, non-comparative	2	Overall response rate	30	13%	N/A	N/A	N/A
Mabthera	102-02-II	Open, multicentre, non-comparative	2	Overall response rate	37	46%	N/A	N/A	N/A
Mabthera	102-05	Open, multicentre, historically controlled	3	Overall response rate	166	48%	N/A	N/A	N/A
Temodal	C94-091	Open, multicentre, randomised	2	Progression-free survival at 6 months	112	21%	Procarbazine[b]	113	8%
Temodal	194-122	Open, multicentre, non-comparative	2	Progression-free survival at 6 months	138	19%	N/A	N/A	N/A
Beromun	152.63	Open, non-comparative	2	Overall response rate	39	62%	N/A	N/A	N/A
Beromun	152.62	Open, multicentre, non-comparative	2	Overall response rate	23	83%	N/A	N/A	N/A
Beromun	152.66	Open, multicentre, non-comparative	2	Overall response rate	23	56%	N/A	N/A	N/A
Beromun	152.12 (interim results)	Open, multicentre, non-comparative	2	Overall response rate	175	65%	N/A	N/A	N/A
Paxene	IX-110-081	Open, multicentre, non-comparative	2	Overall response rate	107	56%	N/A	N/A	N/A
Myocet	1	Open, multicentre, randomised	3	Overall response rate (non-inferiority) plus decrease of LVEF	142	43% (+cyclo phosphamide)	Doxorubicin + Cyclophosphamide	155	43%
Myocet	2	Open, multicentre, randomised	3	Overall response rate (non-inferiority) plus decrease of LVEF	108	26%	Doxorubicin	116	26%
Myocet	3	Open, multicentre, randomised	3	Overall response rate (non-inferiority) plus decrease of LVEF	80	46% (+cyclo phosphamide)	Epirubicin + Cyclophosphamide	80	39%
Herceptin	H0649g	Open, multicentre, non-comparative (monotherapy 2nd/3rd line)	3	Overall response rate	222	15%	N/A	N/A	N/A

Herceptin	H0648g	Open, multicentre, randomised (combination therapy)	3	Time to progression	89	6.9 months (+Paclitaxel)	Paclitaxel alone	89	3.0 months
Targretin	L-1069-23	Open, multicentre, non-comparative	2	Overall response rate	58	34%	N/A	N/A	N/A
Targretin	L-1069-24	Open, multicentre, non-comparative	2	Overall response rate	94	35%	N/A	N/A	N/A
Xeloda	SO-14695	Open, multicentre, randomised	3	Overall response rate (non-inferiority)	302	26%	5-FU/LV Mayo regimen	303	12%
Xeloda	SO-14796	Open, multicentre, randomised	3	Overall response rate (non-inferiority)	301	19%	5-FU/LV Mayo regimen	301	15%
Foscan	08b	Open, multicentre, non-comparative	2	Individual clinical benefit (UWHN questionnaire)	147	22%	N/A	N/A	N/A
MabCampath	CAM211	Open, multicentre, non-comparative	2	Overall response rate	93	33%	N/A	N/A	N/A
MabCampath	005	Open, multicentre, non-comparative	2	Overall response rate	32	28%	N/A	N/A	N/A
MabCampath	009	Open, multicentre, non-comparative	2	Overall response rate	24	33%	N/A	N/A	N/A
Glivec	0102	Open, multicentre, non-comparative (myeloid blast crisis CML)	2	Haematological response rate	260	26%	N/A	N/A	N/A
Glivec	0109	Open, multicentre, non-comparative (accelerated phase CML)	2	Haematological response rate	235	63%	N/A	N/A	N/A
Glivec	0110	Open, multicentre, non-comparative (chronic phase CML)	2	Cytogenetic response rate	532	49%	N/A	N/A	N/A
Trisenox	97-66	Open, single-centre, non-comparative	1/2	Rate of complete remission	12	92%	N/A	N/A	N/A
Trisenox	PLRXAS01	Open, multicentre, non-comparative	2	Rate of complete remission	40	85%	N/A	N/A	N/A
Zevalin	106-04	Open, multicentre, randomised, active-controlled	3	Overall response rate	73	73%	Rituximab	70	47%
Faslodex	9238IL/0020	Open, multicentre, randomised	3	Time to progression (non-inferiority)	222	166 d	Anastrozole	229	156 d
Faslodex	9238IL/0021	Double-blind, multicentre, randomised	3	Time to progression (non-inferiority)	206	165 d	Anastrozole	194	103 d
Velcade	M34100-024	Open, multicentre, non-comparative, randomised	2	Response rate (combined CR + PR + MR)	53 randomised into 2 dose groups	33% (1 mg/m^2) 50% (1.3 mg/m^2)	N/A	N/A	N/A
Velcade	M34100-025	Open, multicentre, non-comparative	2	Response rate (combined CR + PR + MR)	193	35%	N/A	N/A	N/A
Erbitux	EMR 62202-007	Open, multicentre, non-comparative, randomised	2	Overall response rate	329 randomised (2:1) to either combination or mono-therapy	23% (+irinotecan) 11% (mono-therapy)	N/A	N/A	N/A

CML, chronic myeloid leukaemia; CR, complete response; FU, 5-fluorouracil; LV, leucovorin; LVEF, left ventricular ejection fraction; MR, minimal response; N/A, not applicable; PR, partial response; OS, overall survival; RR, response rate; TTP, time to progression; UWHN, University of Washington Head and Neck.

a Overall response rate = complete plus partial remission.

b Treatment not authorised for this indication!.

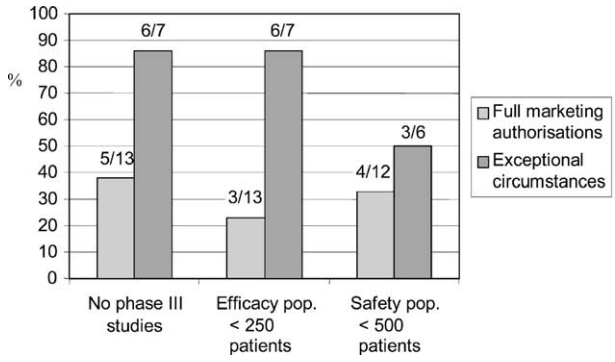

Fig. 2 – Size of clinical data packages for oncology drugs authorised with full marketing authorisations, compared with drugs authorised under exceptional circumstances.

allows a marketing authorisation when – for different reasons (see above) – it is not possible to generate the data which are usually required, e.g. because it would be unethical to do so. Further details on the requirements for a conditional approval will be laid down in a Commission Regulation.

The accelerated evaluation procedure also provides a mechanism for facilitating the marketing authorisation of oncology drugs in the EU. However, the accelerated evaluation procedure was used in only 1 out of the 20 investigated cases. In this single case the accelerated evaluation procedure turned out to be an effective tool for acceleration of approval, resulting in the fastest ever approval of an oncology drug by the EMEA.

Recently, Ericson and colleagues[11] reviewed approval times of a series of AIDS/HIV as well as anticancer agents. Among the seven AIDS/HIV products which have been evaluated by the CPMP after implementation of the EMEA accelerated evaluation guidance,[6] two products were reviewed in an accelerated evaluation procedure (Viread and Fuzeon). The mean time until CPMP opinion was 5.8 months for these two products, whereas the mean time until CPMP opinion was on average 12.1 months for the other five products (Viramune, Viracept, Agenerase, Trizivir and Reyataz). This finding supports the conclusion that the accelerated evaluation procedure is an efficient mechanism to speed up the centralised marketing authorisation procedure in the EU. However, there seems to be a need to make more frequent use of this accelerated evaluation for oncology products.

In this context it is interesting to note that the accelerated evaluation provision has now been included in the new Regulation (EC) 726/2004.[2] Of note, the timeline for accelerated authority review as provided in this Regulation is 150 d and thus longer than the timeline provided in the current EMEA Guidance.[6] This change in the legislative character of the provision, as well as its less stringent timeline, carries at least the hope for its more frequent use in the future for approval of innovative oncology drugs. A comprehensive overview of the recent changes in the legislation is given by Pignatti and colleagues.[13]

It is important to note that the administrative time for all oncology marketing authorisations was above the target duration of 90 d. Thus, for Glivec with a very fast scientific assessment almost half of the overall duration of the marketing authorisation procedure was spent on administrative activities. Such a long duration for the administrative activities is difficult to justify for innovative drugs in the oncology field. It will be interesting to observe whether this time period can be shortened based on the new EU legislation,[2] which stipulates a reduction in the administrative time of 15 d. Apart from this legislative initiative the EMEA information technology project on Product Information Management may help to accelerate the procedures that need to be carried out during this time.[14]

Based on the analysis of the relative duration of the scientific versus the administrative time of the marketing authorisation procedures it may also be worthwhile to consider implementation of an 'accelerated administrative procedure'. Such an 'accelerated administrative procedure' should be used for all drugs that are indicated for treatment of a heavily disabling or life-threatening disease and that have received a positive CHMP opinion. From a patient's perspective it should be possible to achieve, at least for such drugs, a completion of the administrative procedure within 60 d, for example by postponing resolution of issues that are not vital for the patients' safety to a later point in time.

The analysis of the clinical data packages indicates that there is quite some flexibility with respect to the endpoints and trial designs accepted by the EMEA. Even open, non-comparative phase II studies are sufficient in case of outstanding efficacy of a drug (e.g. Beromun, Trisenox). With less efficacy either a randomised, comparative trial or more studies seem to be required (e.g. Temodal, Hycamtin). For compounds which offer a better side-effect profile or improved administration schedules (Fareston, Myocet, Xeloda, Faslodex) versus established drugs, non-inferiority designs can be used in phase III studies to demonstrate a positive risk–benefit ratio. Overall, due to the many different indications covered by the drugs investigated and their different nature (i.e. cytotoxic drugs, hormone antagonists, targeted biotechnological drugs), no further general conclusions on clinical data requirements can be drawn. Additionally, there is a lack of public information on agents that have been withdrawn by the applicant in order to avoid a negative opinion during the CP. Thus, clearly the strategy of choice is to seek clinical scientific advice before embarking on a pivotal clinical trial.

In conclusion, the current EU regulatory framework for the marketing authorisation of oncology drugs provides quite some flexibility with respect to the clinical data requirements. However, the provision for accelerated evaluation of products indicated for serious diseases is not working efficiently and the administrative time needed by the authorities is not supporting a rapid marketing authorisation of oncology drugs. Thus, implementation of the new EU drug legislation clearly offers the opportunity to accelerate the time to market for innovative oncology agents although – based on experience with the current procedures – more effort is likely to be required to achieve this goal.

Conflict of interest statement

None declared.

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