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Between January 2009 and April 2016, 134 novel anticancer therapies were approved: what is the level of knowledge concerning the clinical benefit at the time of approval?

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ABSTRACT

Objective In the last decade an increasing number of high-priced, new cancer treatments received marketing authorisation in Europe. What is actually known about the clinical benefit of those therapies at the time of approval needs to be elucidated in order to inform decisions about the use and reimbursement of these novel treatment options. Thus, the aim of the current analysis was to systematically investigate oncological therapies approved between January 2009 and April 2016 and extract as well as quantify the level of knowledge of the clinical benefit at the time of marketing authorisation.

Methods To assess the benefit of new interventions as well as expanded indications, we extracted the median gain of the two study end points: progression-free survival (PFS) and overall survival (OS). Information is based on approval documents provided by the European Medicines Agency and assessments from the Austrian Horizon Scanning programme. We included all cancer therapies approved in Europe between 2009 (January 1) and 2016 (April 15).

Results Cancer drugs for 134 new indications approved since 2009 were identified. In the case of 37 indications (27%), no data were available for PFS or for OS. A positive difference in median OS was reached by 76 licensed indications (55.5%); 22 (16%) of them showed a difference of more than 3 months. Regarding the study end point PFS, an improvement was shown in 90 indications (65.2%).

Conclusion Scarce knowledge regarding the clinical benefit of anticancer therapies is available at the time of approval. In addition, the survival benefit of the approved indications is less than 3 months in the majority of approved therapies.

Key questions

What is already known about this subject?
- ► High approval rate on the basis of surrogate end points
- ► Many anticancer therapies did not or do not show improved clinically relevant end points
- ► Limited evidence endorsing the positive benefit-risk balance at the time of marketing authorisation in case of conditional approvals
- ► Growing number of fast regulatory approvals

What does this study add?
- ► Overview of approved anticancer therapies between 2009 and 2016 (April) by the European Medicines Agency
- ► Extraction and quantification of the clinical benefit using the difference in median overall survival (OS) and progression-free survival (PFS)
- ► The level of knowledge at the time of approval regarding the difference in median PFS and OS

How might this impact on clinical practice?
- ► Optimise the use of therapies
- ► Prioritise the use of therapies

How might this impact on decision makers and regulatory processes?
- ► Systematic assessment of follow-up trials (on a national level)
- ► Use of a systematic and transparent tool to evaluate the clinical benefit

BACKGROUND

All (western) healthcare systems are challenged by high expenditures for oncological therapies which use a large proportion of hospital drug budgets—with an increasing tendency of the amount spent on high-priced anticancer drugs.[1 2] Moreover, international debate about the actual clinical value and patient benefit of many anticancer therapies as well as criticism about the methodology of approval studies is on the rise.[3] The increased use of surrogate primary end points and the growing number of fast regulatory approvals despite a high degree of uncertainty are the main focus of criticism.[3–8] This is causing increasing concern among key stakeholders.[9–11] International cancer societies, like the European Society of Medical Oncology (ESMO),[12] and the American Society of Clinical Oncology (ASCO),[13] have reacted by developing scoring systems to assess the value of the many new compounds.

These challenges and public debates highlight the need to optimise and prioritise the use of new, expensive therapies and the enormous importance of evidence-based information about the benefit of novel drugs. Therefore, Horizon Scanning Systems (HSS) have been established by a couple of countries (eg, UK, USA, Sweden, Canada and New Zealand). The main focus of these programmes is to provide information for decision-makers about novel treatment options in advance of their initial implementation.[14 15]

One of the leading countries with regard to the early adoption and disposability of new cancer therapies is Austria.[16] This fact raised concern among payers and, as a consequence, the Austrian Ludwig Boltzmann Institute for Health Technology Assessment (LBI–HTA) was commissioned to develop and introduce an early awareness system called 'Horizon Scanning in Oncology' (HSO).[15] Since 2009, 59 LBI-HTA assessments have been conducted and disseminated to all drug commissions in Austrian hospitals.

In May 2016, an agreement between the countries of Belgium, the Netherlands, Luxemburg and Austria (Benelux-A) was signed. This will lead to the implementation of a shared HSS forecasting all expensive drugs and the according early shared price negotiations.[17] Therefore, we conducted a systematic investigation on all anticancer drugs approved by the European Medicines Agency (EMA) between January 2009 and April 2016.[18] The objective of this study was to extract and quantify the knowledge of the clinical benefit of oncological therapies at the time of approval.

MATERIALS AND METHODS

Identification

We included all new anticancer therapies and expanded indications of already approved drugs that received marketing authorisation between 1 January 2009 and 15 April 2016. We excluded supportive drug therapies that are not used as a curative or palliative cancer treatment. Our sources of information were the European Public Assessment Reports published by the EMA (http://www.ema.europa.eu/ema/), and the LBI-HTA HSO documents (http://hta.lbg.ac.at/page/horizon-scanning-in-der-onkologie-berichte/en).

Clinical benefit

Since overall survival (OS) is the gold standard for the demonstration of the clinical benefit and its surrogate parameter progression-free survival (PFS) is the second most commonly used study end point in cancer clinical trials we applied these two study end points to document the clinical benefit of the examined therapies.[19] To evaluate the clinical benefit of oncological therapies we decided to use the difference in the point estimates median OS and PFS, between the control arm and the intervention arm. We agreed upon the median value since it is the least biased estimator of the expected effect.

Data extraction

We extracted the positive or negative differences in point estimates, median PFS and OS in months, between new drugs and the respective controls in the approval studies. If more than one intervention group was tested, each group was taken into account as a separate data value. If the primary or secondary study end point was not reached, not available or not estimable, it was documented in our data set.

Classification

To ensure comparability, we assigned all approved indications into the International Classification of Diseases (ICD, 10th revision) defined by the World Health Organization (WHO). This resulted in 15 different ICD groups; approved indications for more than one ICD–10 category are thus allocated into one combined group (table 1).

Analysis

We analysed the data using Microsoft Office Excel 2010.

RESULTS

ICD–10 categories

We identified 134 different new anticancer therapies and expanded indications that received marketing authorisation between 2009 (1 January) and 2016 (15 April). The majority (N=34) of the approved therapies pertain to the ICD–10 category C81–C96 (blood tissue cancer). The second most commonly approved drugs belong to the C15–C26 (N=22, malignant neoplasms of digestive organs) as well as to the C30–C39 (N=20, lung cancer) category. The categories with sparse novel approvals were C45–C49, C40–C41, C69–C72, D37–D48 and C81–C96 (table 1).

Difference in median OS of individual therapies in the ICD–10 category

A survival benefit of over 3 months in at least 50% of therapies in the respective ICD–10 category was observed in three (C51–C58, C60–C63, C73–C75) of the ICD–10 groups. In six groups the investigated therapies showed a survival prolongation between 0 and 3 months in at least 50% of cases. A negative difference in median OS was associated with the ensuing substances gefitinib, erlotinib, crizotinib (C30–C39), bevacizumab (C51–C58 and C45–C49) and bendamustine (C81–C96) (table 2, figure 1).

The study end point OS was not reached at the time of approval in leastwise 5% (and at most 33%) of the evaluated therapies of six ICD–10 groups. In the groups C43–C44 and C81–C96, one and two of the therapies demonstrated a survival benefit that was not estimable. Five groups comprised therapies where no data regarding median OS were available (table 2).

Difference in median PFS of individual therapies in the ICD–10 category

A positive difference in median PFS of over 3 months in at least 50% of the investigated therapies could be observed in three ICD–10 groups (C45–C49, C51–C58 and C73–C75). In three groups the investigated therapies showed a

Table 1 Anticancer therapies that received marketing authorisation between 1 January 2009 and 15 April 2016 classified in ICD–10 categories—sequenced according to their frequency

International Classification of Diseases 10th revision (ICD–10) (N=134)	N
C81–C96 Malignant neoplasms, stated or presumed to be primary, of lymphoid, haematopoietic and related tissue	34
C15–C26 Malignant neoplasms of digestive organs	22
C30–C39 Malignant neoplasms of respiratory and intrathoracic organs	20
C50–C50 Malignant neoplasm of breast	16
C43–C44 Melanoma and other malignant neoplasms of skin	13
C60–C63 Malignant neoplasms of male genital organs	8
C51–C58 Malignant neoplasms of female genital organs	4
C64–C68 Malignant neoplasms of urinary tract	4
C51–C58 & C45–C49 Malignant neoplasms of female genital organs and malignant neoplasms of mesothelial and soft tissue*	4
C73–C75Malignant neoplasms of thyroid and other endocrine glands	3
D37–D48 Neoplasms of uncertain or unknown behaviour	2
C45–C49 Malignant neoplasms of mesothelial and soft tissues	1
C40–C41 Malignant neoplasms of bone and articular cartilage	1
C69–C72 Malignant neoplasms of eye, brain and other parts of central nervous system	1
D37–D48 and C81–C96 Neoplasms of uncertain or unknown behaviour and malignant neoplasms, stated or presumed to be primary, of lymphoid, haematopoietic and related tissues*	1

* Oncological therapies which received marketing authorisation for an indication that includes diseases which do not belong to the same ICD–10 category were allocated into one combined group of two ICD–10 categories (eg, C51–C58 and C45–C49: ovarian and peritoneal cancer).

prolongation of PFS between 0 and 3 months in at least 50% of the cases. One therapy of each of the two groups C15–C26 and C30–C39 showed a negative difference in median PFS between the intervention arm and the control arm (table 3).

In four ICD–10 groups (C43–C44, C60–C63, C73–C75 and C81–C96) the study end point PFS was not reached by at least one of the included therapies. None of the examined therapies showed a non-estimable result in PFS. In 11 groups, no results concerning the median PFS

Table 2 Difference in median OS of individual therapies per ICD–10 category and difference in overall median OS

ICD–10	N	mOS (m)>3, N (%)	mOS (m) 0–3, N (%)	mOS (m)<0, N (%)	NR, N (%)	NE, N (%)	NA, N (%)
C15–C26	22	3 (14)	16 (73)	0 (0)	2 (9)	0 (0)	1 (4)
C30–C39	20	1 (5)	11 (55)	4 (20)	1 (5)	0 (0)	3 (15)
C40–C41	1	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (100)
C43–C44	14*	3 (21)	5 (36)	0 (0)	2 (15)	1 (7)	3 (21)
C45–C49	1	0 (0)	1 (100)	0 (0)	0 (0)	0 (0)	0 (0)
C50–C50	16	3 (19)	5 (31)	0 (0)	2 (12)	0 (0)	6 (38)
C51–C58	4	2 (50)	2 (50)	0 (0)	0 (0)	0 (0)	0 (0)
C51–C58 & C45–C49	5*	2 (40)	2 (40)	1 (20)	0 (0)	0 (0)	0 (0)
C60–C63	8	5 (62)	2 (25)	0 (0)	0 (0)	0 (0)	1 (13)
C64–C68	4	0 (0)	3 (75)	0 (0)	0 (0)	0 (0)	1 (25)
C69–C72	1	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (100)
C73–C75	3	2 (67)	0 (0)	0 (0)	1 (33)	0 (0)	0 (0)
C81–C96	34	1 (3)	5 (15)	1 (3)	7 (20)	2 (6)	18 (53)
D37–D48	2	0 (0)	1 (50)	0 (0)	0 (0)	0 (0)	1 (50)
D37–D48 & C81–C96	2*	0 (0)	1 (50)	0 (0)	0 (0)	0 (0)	1 (50)
N (%)	137 (100)	22 (16.1)	54 (39.4)	6 (4.4)	15 (11)	3 (2.1)	37 (27)

*one compound of the respective group was included two times, because in the approval study two intervention groups were tested; therefore, each intervention group was taken into account as a separate data value. Due to the higher number of interventions groups in some studies, the total number of therapies has increased from 134 to 137.
mOS (m), difference in median OS (months) between the intervention arm and the respective control arm; >3, positive difference in median OS of over 3 months; 0–3, positive difference in median OS of 0 to 3 months; <0 negative difference in median OS; NA, no data for median OS were available; NE, median OS was not estimable; NR, median OS was not reached; ICD, International Classification of Diseases.

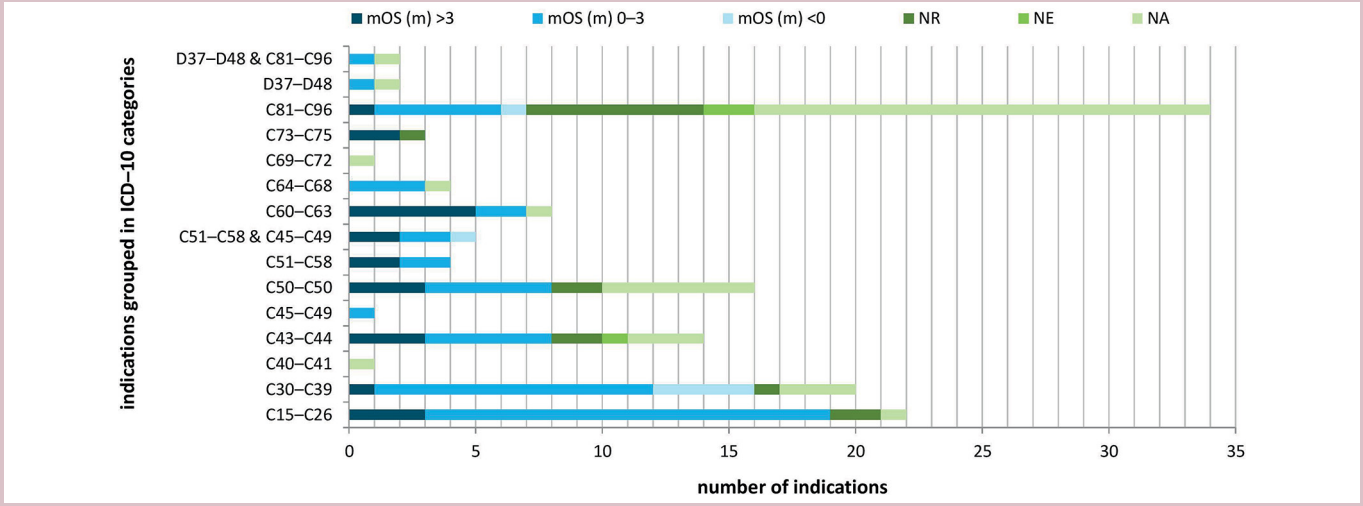

Figure 1 Difference in median overall survival (OS) (months) of individual therapies per International Classification of Diseases 10th revision (ICD–10) category (*N*=137). mOS (m), difference in median OS (months) between the intervention arm and the respective control arm; NA, no data for median OS were vailable; NE, median OS was not estimable; NR, median OS was not reached.

(table 3, figure 2) were available for at least 25% (and at the most 100%) of the approved therapies.

Difference in overall median OS

Twenty-two (16% of all) therapies were associated with a positive median OS difference of over 3 months. The maximum survival prolongation obtained by one compound was 15.7 months (see online supplementary table S1. In the majority of the approved therapies (*N*=54, 39%), a positive OS difference of between 0 and 3 months could be observed. Six (5%) therapies showed a negative difference in median OS compared with the control arm. The study end point OS was not reached by 15 therapies (11%); three therapies showed no estimable OS data (2%). Data for median OS were not available in

Table 3 Difference in median PFS of individual therapies per ICD–10 category and difference in overall median PFS

ICD–10	N	mPFS (m)>3, N (%)	mPFS (m) 0–3, N (%)	mPFS (m)<0, N (%)	NR, N (%)	NE, N (%)	NA, N (%)
C15–C26	22	5 (23)	14 (64)	1 (4)	0 (0)	0 (0)	2 (9)
C30–C39	20	5 (25)	9 (45)	1 (5)	0 (0)	0 (0)	5 (25)
C40–C41	1	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (100)
C43–C44	13	5 (38)	3 (23)	0 (0)	1 (8)	0 (0)	4 (31)
C45–C49	1	1 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
C50–C50	16	6 (38)	5 (31)	0 (0)	0 (0)	0 (0)	5 (31)
C51–C58	4	0 (0)	3 (75)	0 (0)	0 (0)	0 (0)	1 (25)
C51–C58 and C45–C49	5*	3 (60)	2 (40)	0 (0)	0 (0)	0 (0)	0 (0)
C60–C63	8	2 (25)	2 (25)	0 (0)	1 (12)	0 (0)	3 (38)
C64–C68	4	1 (25)	3 (75)	0 (0)	0 (0)	0 (0)	0 (0)
C69–C72	1	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (100)
C73–C75	3	2 (67)	0 (0)	0 (0)	1 (33)	0 (0)	0 (0)
C81–C96	37†	13 (35)	6 (16)	0 (0)	3 (8)	0 (0)	15 (41)
D37–D48	2	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (100)
D37–D48 and C81-C96	1	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (100)
N (%)	138 (100)	43 (31.1)	47 (34.1)	2 (1.5)	6 (4.3)	0 (0)	40 (29)

* one compound of the C51–C58 and C45–C49 groups was included two times, because in the approval study two intervention groups were tested; therefore, the two groups were taken into account as a separate data value.
† two compounds of the C81–C96 group were included several times, because in the approval study two or three intervention groups were tested; therefore, these intervention groups were taken into account as a separate data value. Due to the higher number of interventions groups in some studies, the total number of therapies has increased from 134 to 138.
mPFS (m), difference in median PFS (months) between the intervention arm and the respective control arm;>3, positive difference in median PFS of over 3 months; 0–3, positive difference in median PFS of 0 to 3 months;<0 negative difference in median PFS; NA, no data for median PFS were available; NE, median PFS was not estimable; NR, median PFS was not reached; ICD, International Classification of Diseases.

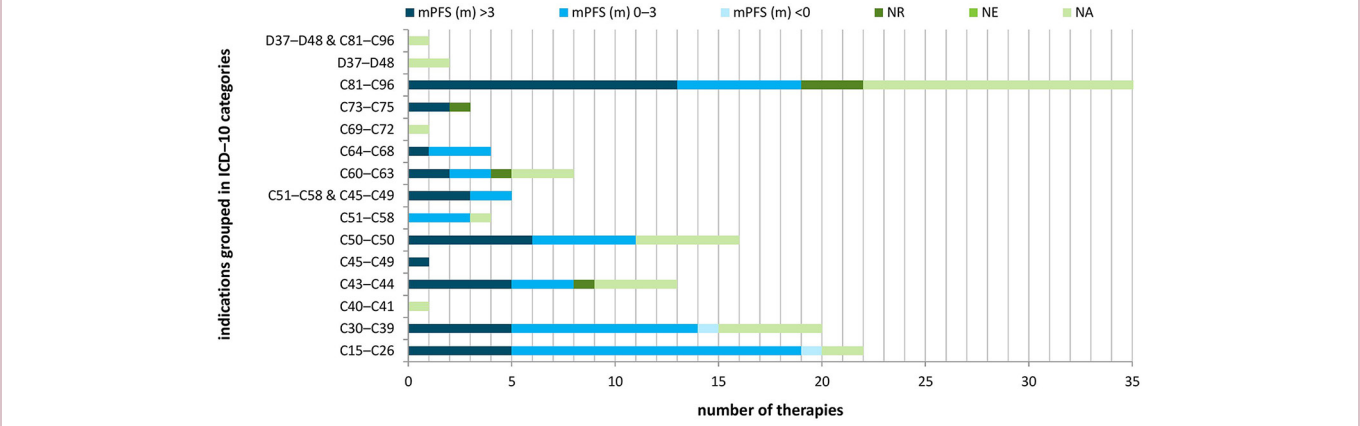

Figure 2 Difference in median progression-free survival (PFS) (months) of individual therapies per International Classification of Diseases 10th revision (ICD–10) (*N*=138). mPFS (m), difference in median PFS (months) between the intervention arm and the respective control arm; NA, no data for median PFS were available; NE, median PFS was not estimable; NR, median PFS was not reached.

37 interventions (27%) (table 2, see online supplementary figure S1).

Difference in overall median PFS

A positive difference in median PFS of over 3 months could be observed in 43 therapies (31%); the highest PFS positive difference obtained by one compound was 22.5 months (see online supplementary table S1). Two of the investigated therapies (1.5%) demonstrated a negative difference in PFS compared with the control arm. The study end point PFS was not reached by six of the identified therapies (4.3%) and no data of median PFS were available for 40 therapies (29%) (table 3, see online supplementary figure S1).

DISCUSSION

In total, cancer drugs for 134 new indications were approved between January 2009 and April 2016, of which a fourth (*N*=34, 25%) are indicated for blood tissue cancer. For 37 indications (27%) no data were available for PFS and OS at the time of approval. A positive difference in median OS was associated with 76 licensed indications (55.5%); for 22 (16%) of them a prolongation of more than 3 months could be observed. A positive difference in median PFS was observed in 90 indications (65.2%); 43 (31%) of them showed a positive difference of more than 3 months. In six indications (4.4%) a decrease in median OS was reported.

Our findings indicate that in a large number of therapies no valid knowledge about the survival benefit is available at the time of approval. For more than a quarter of the approved anticancer therapies since 2009 no data were available for median OS or for median PFS. In the minority of cases a positive difference in median OS of over 3 months was associated.

The main limitation of our analysis was that follow-up data were not considered. Medium-term to long-term studies with hard end points after the approval of a certain therapy are being performed for most drugs.[20] This would be of particular interest, since novel drugs are more and more often approved on an accelerated pathway.[3] Further on, we only documented two efficacy end points and did not record additional end points like disease-free survival DF or patient reported outcomes. Another limitation is that the median values may be influenced by chance. However, this is even more likely for the boundaries of the CIs; these are heavily affected by the sample size and the deviation of the variable of interest. Therefore, the use of HRs could be a further option to determine the clinical benefit of drugs.

The fact that a wide choice of therapies provides a minimal incremental benefit compared with acceptable standard therapy for high costs (marginal medicine)[21] highlights the importance of a prioritised use of oncological therapies. In countries like Germany, England or Sweden, different methodologies have already been applied to regulate reimbursement policies for new treatment options.[22–24] Two instruments—managed entry agreements and value-based pricing—are options that are implemented ever more often to facilitate access to new therapies under uncertainty and to enforce pricing regulations.[24–27]

In the last decade, several other authors have analysed high-priced anticancer drugs and their clinical benefits at the time of approval.[2 21 28] A 2015 study[10] showed that there is no correlation between survival improvements and the costs of anticancer therapies. In addition, due to the approval of drugs at an early stage the impact is often overestimated, respectively, the risk for serious adverse events underestimated.[3 4] In 2006, some authors[29] evaluated the added value of EMA-approved anticancer drugs used for haematological malignancies. About a third of the drug applications showed no added value, either because of end point robustness and/or for methodological reasons.

In general, threshold requirements for therapy decisions differ in the areas of application, implication

and licensing. Clinicians are interested in the potential benefit for individual patients and the burden of side effects, whereas reimbursement decisions are rather based on the relative effectiveness and the predicted future costs of a specific therapy (value for money).[4] Regulatory agencies on the other hand decide upon the risk-benefit balance of each therapy at the time of marketing authorisation. However, only recently, regulators—being criticised for drug approvals based on limited evidence—proposed the concept of 'adaptive pathways' to manage risk and uncertainty after early approvals.[30]

To evaluate the benefit of oncology drugs, tools are provided by professional organisations (eg, ASCO, ESMO).[12 13] These scales are highly appreciated[31] and can be approached to support the assessment of the patient-relevant clinical benefit of oncology drugs. Further, the exchange of information, methodology and the joint development of tools on an European level between regulators (EMA), HTA networks (eg, European network of Health Technology Assessment, EUnetHTA) represented by scientific institutes (eg, Institute for Quality and Efficiency in Health Care, IQWiG; National Institute for Health and Care Excellence, NICE) can support the alignment of perspectives and sustainable evidence-based decisions for healthcare systems.[32]

Our findings in combination with recent studies emphasise the need for a systematic tool to evaluate the benefit of novel drugs in a standardised and transparent way, as well as the importance of the systematic assessments of follow-up trials 3–6 years after approval of all anticancer drugs on a national level.

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