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Original Research

Monitoring evidence on overall survival benefits of anticancer drugs approved by the European Medicines Agency between 2009 and 2015

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Abstract ***Objective:*** The introduction provisional approval strategies increases the approval of anticancer drugs with ambiguous benefit-risk profiles. Thus, in many instances, there is lacking evidence about overall survival (OS) at the time of marketing authorisation. Our objective was to monitor and characterise therapies with ambiguous benefit-risk profiles and identify any postapproval updates on median OS after at least 3 years of approval by the European Medicines Agency (EMA).
Methods: We included all originator anticancer drugs with initially ambiguous benefit-risk profiles that received marketing authorisation by the EMA between January 1, 2009 and May 31, 2015. Our monitoring timeframe was at least 3 years after EMA approval. To identify study updates, the following three sources were included: clinicaltrials.gov, European Public Assessments Reports and PubMed.
Results: In total, we identified 102 eligible approval studies. Out of these, a negative difference in median OS or no information was available in 43 (42.2%) instances. During monitoring, 14 updates with accessible positive information on OS could be identified. Including monitoring results, there are still 29 remaining therapies (28.4%) where no or negative information ($n = 24$ [23.5%] and $n = 5$ [4.9%], respectively) regarding OS is present at least 3 years after EMA approval.
Conclusion: One-third of oncology drugs with ambiguous benefit-risk profiles at the time of approval fail to demonstrate a survival benefit even after several years of marketing

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authorisation. Systematic and transparent postapproval monitoring mechanisms will be of high relevance to assure a clinically relevant patient benefit, since the trend towards faster access to medicines with uncertain benefit is increasing rather than declining.

1. Introduction

Scarcity of longer-term outcome evidence for oncological therapies at the time of regulatory approval has become a major issue affecting many health-care stakeholders [1–4]. The gold standard measurements for the clinical benefit of cancer drugs are clinically meaningful improvements in overall survival (OS), quality of life (QoL), and/or toxicity profile [5]. Generally, marketing authorisations have to be based on a benefit-risk assessment, in which a benefit clearly outweighs the risks of a drug [6–8]. The European Medicines Agency (EMA) has stated that a demonstrated advantageous OS effect is clinically and methodologically the most convincing outcome of a clinical study [6]. Thus, approvals should ideally depend on a favourable OS profile and not on any surrogate parameters [9]. However, because of the increasing number of provisional licensing strategies, approvals are more and more commonly based on ambiguous benefit-risk profiles [10,11].

Since 2006, the EMA has introduced the conditional approval pathway that allows marketing authorisations to be granted on the basis of limited evidence, especially to satisfy unmet medical demands of patients and overall public health priorities [2,12]. Between 2006 and 2016, 30 conditional marketing authorisations had been granted under specific postauthorisation obligations, which were most commonly final results from clinical studies (70%) but also included interim results of ongoing trials (10%), other measures (9%, not further specified) and additional studies (7%) [13,14]. More than half of these therapies ($n = 17$, 57%) were indicated for the treatment of cancer [13]. Although under this scheme clear obligations are given to the marketing authorisation holders, these are often delayed or only partially fulfilled/reported. Nevertheless, the approval status usually remains [2].

The trend to allow constantly faster access to drugs with ambiguous benefit-risk profiles via conditional approval pathways leads to smaller, shorter and less cost-intensive trials and an increasing use of surrogate primary end-points [2,7]. This also applies for clinical studies of orphan drugs that often encompass methodological concerns and deficits in the reporting of results, even though these drugs receive a prolonged market exclusivity [15]. Additionally, initially approved drugs with limited evidence at the time of marketing authorisation may receive a label for 'under additional monitoring'. This label should in turn lead to a more intensive monitoring in the postapproval phase and enhance the reporting of any adverse drug reactions. This shall assure that the benefits of medicines continue to outweigh their risks [16]. In addition to the aforementioned accelerated licensing strategies, two further pathways (adaptive pathways and PRIority MEdicines) which shall allow early and thereby faster patient access have been introduced by the EMA [17]. All these faster access routes increase the chance of allowing drugs onto the market that are potentially ineffective or unsafe and thereby may pose a risk to public health.

Therefore, our aim was to identify how much monitoring evidence on median OS of oncology drugs with initially ambiguous benefit-risk profiles—defined as drugs where no or negative information on median OS was available at the time of approval—is accessible at least 3 years after marketing authorisation. In addition, we synthesised the characteristics of this study cohort including its EMA labels.

2. Methods

2.1. Identification of the study cohort

We included originator anticancer drugs that were approved by the EMA between 1 January 2009 and 31 May 2015. Out of this cohort, we selected those drugs with ambiguous benefit-risk profiles, where no or negative information on median OS was available at the time of approval. Two former studies were used as a basis for the identification of the study cohort [18,19]. Besides the website of the EMA, the European Public Assessments Reports (EPARs) were used as sources of information. As a time interval for possible study updates, the period of at least 3 years after EMA approval was chosen.

2.2. Identification of study updates and data extraction

The following three sources were included in our investigation to identify study updates: ClinicalTrials.gov (https://clinicaltrials.gov/), EPARs and PubMed. PubMed was used to perform a systematic literature search for each approval study with the terms '(name of the active substance) AND (NCT number OR trial

name)' with no limitations (Supplementary Figure A.1). The systematic search in all databases was conducted between 19 January and 1 June 2018. The ClinicalTrials.gov registry number, 'NCT' number, was applied to properly link approval studies to their respective study updates. Main information on the study updates, the absolute median OS and the difference of median OS between the study groups were extracted by one author (N.G.). In addition, information on the hazard ratio (HR) of death and its confidence intervals (CIs) were extracted. Both the identification of study updates and the extraction of data were performed by another author (M.R.), whereby disagreements were reviewed and examined jointly (N.G. & M.R.). Beside a positive difference in median OS, a statistically significant difference in OS as well as the 95% CI of the HR of death does not cross the null value were considered as positive OS information.

2.3. Data extraction

Extracted data were collected into a Microsoft Office Excel 2010 data form *a priori*-designed by the study team.

3. Results

3.1. Characteristics of the approval studies

In total, we identified 105 approval studies. This resulted in 102 eligible studies since three trials were excluded because of lack of information on the NCT number. Indications were most commonly approved for the treatment of lymphoid, haematopoietic and related tissue tumours (n = 31 [30.4%]), gastrointestinal tumours (n = 15 [14.7%]) and breast cancer (n = 13 [12.8%]) (Table 1). Out of these, 54 (52.9%) therapies had either been under additional monitoring, were granted a

Table 1
Characteristics of EMA-approved therapies (Jan 2009–May 2015) at the time of approval and ≥3 years after approval.

Characteristics	All approved therapies (n = 102)	Missing/negative median OS data at the time of approval (n = 43 [42.2%])	Missing/negative OS data ≥3 years after approval (n = 29 [28.4%])
Indication (ICD-10 category)			
All solid cancer therapies	71 (69.6%)	20 (46.5%)	13 (44.8)
Gastrointestinal cancer (C15–C26)	15 (14.7%)	4 (9.3%)	3 (10.3%)
Lung cancer (C30–C39)	11 (10.8%)	5 (11.6%)	3 (10.3%)
Melanoma (C43–C44)	7 (6.9%)	2 (4.7%)	–
Sarcoma (C45–C49)	1 (0.9%)	–	–
Breast cancer (C50–C50)	13 (12.8%)	3 (7.0%)	1 (3.4%)
Cervical carcinoma (C51–C58)	2 (2.0%)	–	–
Ovarian & peritoneal cancer (C51–C58 & C45–C49)	6 (5.9%)	2 (4.7%)	2 (6.9%)
Prostate cancer (C60–C63)	7 (6.9%)	1 (2.3%)	1 (3.4%)
Renal cell carcinoma (C64–C68)	5 (4.9%)	–	–
Thyroid carcinoma & neuroendocrine tumour (C73–C75)	4 (3.9%)	3 (7.0%)	3 (10.3%)
Lymphoid, haematopoietic and related tissue cancer (C81–C96 & D37-D48)	31 (30.4%)	23 (53.5%)	16 (55.2%)
Approval year			
2009	15 (14.7%)	8 (18.6%)	7 (24.1%)
2010	17 (16.7%)	6 (14.0%)	3 (10.3%)
2011	17 (16.7%)	5 (11.6%)	3 (10.3%)
2012	15 (14.7%)	4 (9.3%)	2 (6.9%)
2013	17 (16.7%)	8 (18.6%)	4 (13.8%)
2014	15 (14.7%)	7 (16.3%)	6 (20.7%)
2015	6 (5.9%)	5 (11.6%)	4 (13.8%)
EMA approval/designation			
Additional monitoring (AM)	40 (39.2%)	22 (51.2%)	16 (55.2%)
Conditional approval (CA)	17 (16.7%)	6 (14.0%)	3 (10.3%)
Orphan designation (OD)	22 (21.6%)	14 (32.6%)	10 (34.5%)
AM & CA	3 (2.9%)	2 (4.7%)	2 (6.9%)
AM & OD	10 (9.8%)	8 (18.6%)	6 (20.7%)
CA & OD	2 (2.0%)	–	–
AM & OD & CA	4 (3.9%)	2 (4.7%)	1 (3.4%)
No specific EMA approval/designation	48 (47.1%)	15 (34.9%)	11 (37.9%)
Information on median OS			
Positive median OS data	59 (57.8%)	–	–
Negative median OS data	5 (4.9%)	5 (11.6%)	5 (17.2%)
No median OS data available	38 (37.3%)	38 (88.4%)	24 (82.8%)

EMA, European Medicines Agency; ICD-10, International Classification of Disease (10th Revision); OS, overall survival.
Data are n (%) unless otherwise specified. Deviation of 100% cumulative percentage may be caused by rounding.

conditional marketing authorisation or had received orphan designation by the EMA.

3.2. Availability of evidence on median OS at the time of approval

In 43 instances out of the 102 investigated therapies (42.2%), either evidence of a negative difference in median OS (n = 5 [4.9%]) or no information regarding this study end-point (n = 38 [37.3%]) was available at the time of approval resulting in an ambiguous benefit-risk profile (Table 1). The remaining 59 therapies (57.8%) had positive data on median OS available. Out of the 43 therapies with ambiguous benefit-risk profiles at the time of approval, 28 (65.1%) received a special label by the EMA (supplementary Table A.1). Among the total 32 labels (some therapies received double labels), 17 (53.1%) were for additional monitoring, three (9.4%) for initially conditional marketing authorisation and 11 (34.4%) for the treatment of orphan diseases.

In total, 71 (69.6%) EMA-approved therapies were indicated for the treatment of solid tumours; out of those, there was no or negative evidence regarding median OS at the time of approval in 20 (28.2%) cases (Fig. 1). Among the 31 lymphoid, haematopoietic and related tissue cancer drugs, no or negative information regarding median OS at the time of approval was present in more than two-thirds (n = 23 [74.2%]) (Fig. 1).

3.3. Monitoring of evidence—availability of positive OS information at least 3 years after EMA approval

During monitoring, updates for 27 (n = 27/43 [62.8%]) different therapies with initially missing or negative median OS data were identified. Out of these, only 11 (n = 11/43 [25.6%]) exhibited positive monitoring information on median OS. Additionally, three (n = 3/43 [7.0%]) therapies offered positive information on the CIs of HRs of death and/or a statistically significant differences in OS.

Including the identified monitoring updates after at least 3 years of EMA approval (n = 114), positive OS data were available in 73 (71.6%) out of the 102 instances, while in 29 cases (28.4%), no or negative information (n = 24 [23.5%] and n = 5 [4.9%], respectively) regarding OS was publicly accessible (Fig. 1). Of the five therapies where negative initial information on median OS was available at the time of approval, three offered study updates after EMA authorisation. Among these, positive benefit in median OS in the overall study population was demonstrated in one instance (Table 1, supplementary Table A.1). In addition, one update showed a positive difference in median OS in a specific genomic subpopulation of the trial. In one instance, where initially no information on median OS was available, an update led to a negative difference after monitoring. With respect to those therapies that were initially authorised under conditional approval (n = 17), 11 therapies have shown an OS benefit after monitoring.

Most therapies with ambiguous benefit-risk profiles following an at least 3-year monitoring period (n = 29) were approved in 2009 (n = 7 [24.1%]) or 2014 (n = 6 [20.7%]); more than half of which were indicated for the treatment of lymphoid, haematopoietic and related tissue tumours (n = 16/32 [55.2%]). Considering all lymphoid, haematopoietic and related tissue tumour drugs (n = 31), there was a lack of published evidence on positive OS in about half of these 3 years or more

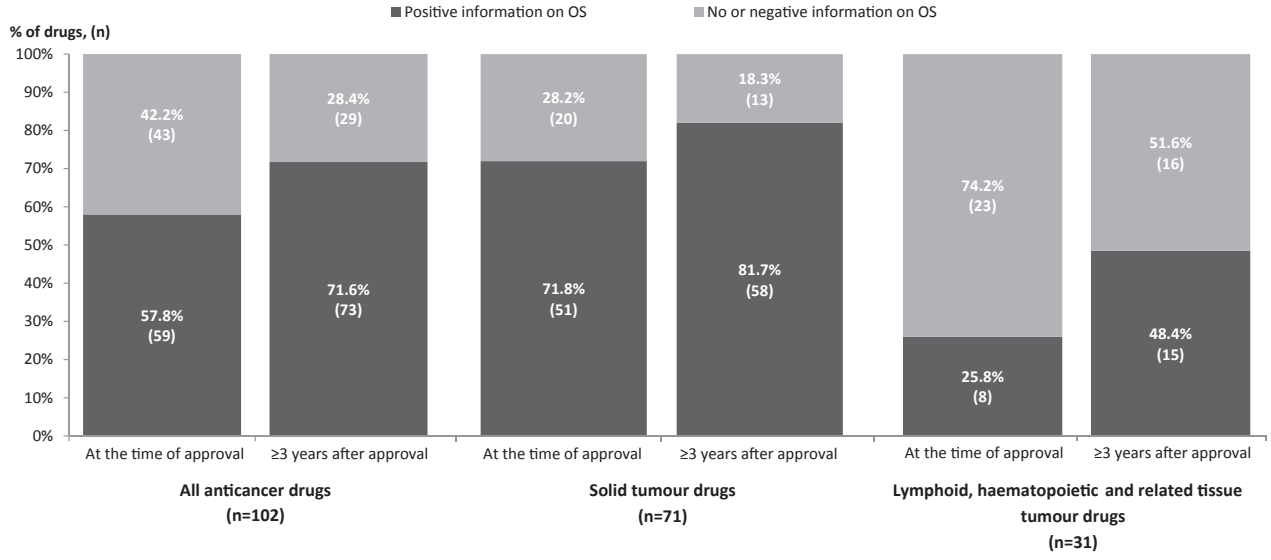

Fig. 1. Availability of evidence on overall survival for EMA-approved oncology drugs at the time of marketing authorisation and after at least 3 years of approval.
OS, overall survival; EMA, European Medicines Agency.

after approval (n = 16 [51.6%]) (Fig. 1). On the other hand, 13 (44.8%) of the 29 therapies with ambiguous benefit-risk profiles 3 years or more after approval were for the treatment of solid tumours (Table 1). Out of the 71 solid tumour drugs, positive information on OS at least 3 years after marketing authorisation was available in 81.7% (n = 58/71) of instances, including seven updates that were identified during monitoring. The other 18.3% (n = 13/71) of solid tumour therapies had no or negative information on median OS postapproval (Fig. 1).

4. Discussion

In our study, we sought to investigate the availability of follow-up evidence on median OS at least 3 years after EMA approval, focusing on those therapies with ambiguous benefit-risk profiles at the time of European market entrance. In total, we identified 102 eligible therapies that were EMA-approved between January 2009 and May 2015. Despite the fact that there is considerable evidence generated and published after EMA authorisation, there is still a lack of information on OS in about one-third of all the identified therapies (n = 29 [28.4%]), which corresponds to 67.4% [n = 29/43] of the drugs with initially no positive median OS evidence at the time of approval. Concurrently, more than one half of these drugs were indicated for lymphoid, haematopoietic and related tissue tumours (n = 16 [55.2%]) and have received a specific label or underwent a particular approval pathway by the EMA (n = 19 [65.5%]). Furthermore, none of these drugs have been withdrawn from the European pharmaceutical market, notwithstanding the fact there is no or even negative information on median OS publicly available after at least 3 years of marketing authorisation [20].

It is commonly asserted that showing OS benefit will take considerable time. Therefore, surrogate end-points, such as minimal residual disease or progression-free survival, are widely used and may be one of the reasons for the higher rate of missing median OS data in the area of lymphoid, haematopoietic and related tissue tumours [21,22]. Overall, our results strengthen the need for a prolonged monitoring period after EMA approval. A drug could theoretically be also tested in a later treatment line or salvaged in a relapsed setting where OS could be shown more rapidly.

Since the introduction of personalised medicine, benefits from anticancer treatments could be increasingly limited to a specific subpopulation [23]. Therapies may offer no positive treatment effect in the overall population but only in a subset of patients. This has to be also considered when interpreting our results. In our sample, it occurred once that the initial overall trial results regarding OS were negative, but the prespecified subpopulation analysis showed a prolonged difference in median OS. Although this evidence on limited benefit was published, the EMA-approved indication has not been restricted to the specific patient population or amended in other relevant ways. Since similar evidence may become present in many other cancer trials, a systematic, prespecified investigation of subgroup effects may be of benefit. However, it has to be considered that the interpretation of these results remains limited because they can be influenced by many methodological issues, such as reduced statistical power and increased variance [24].

To evaluate the clinical benefit of anticancer drugs, both relative-benefits (HR) and absolute-benefits (median) in OS are commonly reported [25,26]. Other survival parameters, especially in cases where a large benefit for a few patients is expected, are absolute and proportional gains in the long-term survival rates [26]. Since in our main analysis we have focused on median OS values, we could have missed evidence available on other OS-related parameters. Therefore, in a sensitivity analysis, we have also examined evidence available on other OS-related parameters in the identified updates. This resulted in nine further studies where some OS-related parameters were accessible (HR: n = 3, OS rates: n = 6). Out of these six cases with data on OS rates, in three instances, there were no differences between the treatment arms, and in two instances, these were from single-arm studies, therefore, not directly comparable. In addition, the three therapies where only HRs were available were approved between 2014 and 2015. Thus, for these three trials not only would a longer follow-up study period be needed but also a prolonged monitoring time after approval is required.

Increasing uncertainty about the clinical benefit of oncology drugs at the time of approval and post-authorisation is a major challenge for health-care policy-makers which has been investigated in many recent studies [1,3,4,7,18,19,27]. Thus, a study from the United States has shown that 67% of marketing authorisations by the Food and Drug Administration were performed on the basis of surrogate end-points [4]. That study also showed that with a median 4.5 years market time, only five of 36 drugs later showed OS benefit, a finding our article confirms. On the other hand, Banzi *et al.* [2] showed that 26 EMA-approved therapies received conditional approval between January 2006 and June 2015. Out of those 14, most common oncology drugs (n = 9) could not fulfil their obligations. Our results are in line with these studies and also with a study from Davis *et al.* [7], where they could observe that in many cases there is limited knowledge on survival after and at the time of approval. As opposed to former studies, our study included therapies for a broad marketing authorisation interval independent of their approval pathways or

indications and systematically monitored and characterised drugs with ambiguous benefit-risk profiles.

The main limitation of our analysis is the chosen timeframe of 'at least 3 years after approval', which may be too narrow to identify possible survival updates for some therapeutic areas. However, taking the years 2009 until 2013 ($n = 81$) into account, there would be still a lack of median OS data in about 26% ($n = 21$) of instances. Moreover, a similar timeframe was used in another study that investigated the postapproval clinical benefit of cancer drugs [7]. Additionally, our results could be influenced by a publication bias, especially a positive-results or outcome reporting bias of follow-up results could be present. Negative trial results could be particularly affected because consequently therapies could be taken off the market [15,28]. Finally, we did not address other patient-relevant end-points such as QoL or adverse events, which would be an appropriate next step in regard to oncology drug monitoring.

In summary, considerable proportion of oncology drugs with ambiguous benefit-risk profiles fail to demonstrate a survival benefit several years after EMA approval. In most of these cases, there is limited evidence about survival at the time of marketing authorisation to start with, which is mostly the result of accelerated authorisation pathways. The low level of publicly available longer-term OS evidence, however, mostly relate to the lack of efficient postlicensing monitoring strategies. Although fast accessibility of drugs, especially for diseases with high unmet needs, plays an important role in an equitable health-care system, ineffective drugs should not remain on the market [4]. To fulfil both prioritisation needs, there should be an implementation of systematic, transparent and automated monitoring and publication mechanisms for all new drugs to assure maximum public health benefits while reducing any potential health hazards.

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Conflict of interest statement

None to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2018.12.026.

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