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Original Research

Five years of EMA-approved systemic cancer therapies for solid tumours—a comparison of two thresholds for meaningful clinical benefit

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Abstract *Objective:* Several societies have proposed frameworks to evaluate the benefit of oncology drugs; one prominent tool is the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS). Our objectives were to investigate the extent of European Medicines Agency (EMA)-approved cancer drugs that meet the threshold for 'meaningful clinical benefit' (MCB), defined by the framework, and determine the change in the distribution of grades when an adapted version that addresses the scale's limitations is applied. *Methods:* We identified cancer drugs approved by the EMA (2011–2016). We previously proposed adaptations to the ESMO-MCBS addressing its main limitations, including the use of the lower limit of the 95% confidence interval in assessing the hazard ratio. To assess the MCB, both the original and adapted ESMO-MCBS were applied to the respective approval studies.

Results: In total, we identified 70 approval studies for 38 solid cancer drugs. 21% of therapies met the MCB threshold by the original ESMO-MCBS criteria. In contrast, only 11% of therapies met the threshold for MCB when the adapted ESMO-MCBS was applied. Thus 89% and 79% of therapies did not meet the MCB threshold in the adapted and original ESMO-MCBS, respectively.

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Conclusions: In most of the cancer drugs, the MCB threshold is not met at the time of approval when measured using both ESMO-MCBS scales. Since approval status does not translate into a MCB, stakeholders and decision makers should focus on the benefit/risk ratio of anticancer drugs to assure an appropriate allocation of resources in health care systems. © 2017 The Author(s). Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

1. Introduction

With the introduction of new fast-track approval pathways for modern anticancer therapies, there are increasing uncertainties and limited evidence regarding the clinical benefit of these drugs at the time they are approved [1,2]. Between 2006 and 2015, 26 drugs, including 14 anticancer therapies, have received conditional marketing authorisation in Europe, despite ambiguous benefit-risk profiles [1]. Two additional accelerated licensing strategies were recently piloted by the European Medicines Agency (EMA)—an adaptive pathway and PRIME (PRiority Medicines)—that allow for faster access to medicines [3]. Such regulatory changes have profound impacts on national medicine and cancer budgets, as well as the ability of health technology appraisal mechanisms to reach evidence-based decisions.

In addition, cancer drug approvals based on surrogate outcomes have become more commonplace [4], lowering clinical trial costs, participant numbers, and follow-up times [5,6], but often still require post-marketing assessments of overall survival (OS) and quality of life (QoL) [1,4]. And, although these studies are often delayed or fail to fulfil their obligations, the approval status remains firm [2,5,6]. Thus, surrogate outcomes lead to faster medicine access, but poor correlations with clinical benefit [1,2,4,7].

In recent years, a variety of frameworks were published to assess the value of cancer treatments. The European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) attempts to support the optimal use of limited health care resources, while offering a standardised and transparent tool to evaluate the benefit of novel cancer therapies [8]. Recently, the ESMO-MCBS has been applied in several studies, and an adapted version was proposed for the use in the area of Health Technology Assessment (HTA) [9–11].

Therefore, our objectives were to (1) evaluate the extent of recently EMA-approved cancer drugs that satisfy the ESMO-MCBS criteria for a ‘meaningful clinical benefit’ (MCB) and (2) contrast these definitions of MCB with the adapted ESMO-MCBS, addressing limitations that were previously identified [10,12,13].

2. Methods

2.1. Identification of approval studies

We included all approval studies of cancer drugs indicated for solid tumours that received marketing authorisation by the EMA between 1st January 2011 and 31st December 2016. The identification of the study cohort was based on a former study that extracted all anticancer drugs approved between January 2009 and April 2016 [14]. However, we updated this list and incorporated all cancer drugs approved for solid tumours since 15th April 2016 until the end of December 2016 by using the European Public Assessment Reports (EPARs) published by the EMA (<http://www.ema.europa.eu/ema/>). The EPARs were also used as a source of information regarding the identification of the respective approval studies. We excluded the following studies that fail to meet the inclusion criteria for use by ESMO-MCBS [8]: single-arm studies, cancer drugs for non-solid tumours, generics, studies with non-statistically significant results and studies with end-points not amenable for scoring by ESMO-MCBS (Supplementary Fig. A.1).

2.2. Data extraction and scoring

One author (NG) extracted and compiled efficacy data as well as information on QoL and toxicities from the published approval studies and the respective EPARs. Subsequently, two authors (SW and JDP) assessed the extracted data independently and blindly. Any disagreements were reviewed and examined by the blinded authors (NG, SW and JDP).

Two different ESMO-MCBS scales were applied to the results of all identified approval studies ($n = 70$): the original ESMO-MCBS published by Cherny *et al.* [8] and an adapted framework of the ESMO-MCBS for utilisation in HTA practice [10]. In the adapted framework, modifications of the original ESMO-MCBS were applied, as outlined in Table 1 and Table A.4. In both scales, only statistically significant end-points were graded. Based on the subsequent order, one of the following study end-points was used to generate an ESMO-MCBS grade:

Table 1

Modifications of the original ESMO-MCBS that attempt to address shortfalls of the framework.

Adapted ESMO-MCBS	Original ESMO-MCBS
Generation of grades	
Point estimate of the HR used	Lower limit of the 95% CI of the HR used
Grade adjustments	
<i>Downgrades</i> due to a negative median OS despite graded end-point showing a statistically significant, positive difference (Forms 2a, b and c)	<i>Not implicated</i>
<i>Downgrades or upgrades</i> due to positive or negative differences, respectively, of at least 10% in any grade ≥ 3 AEs (Forms 2a and b)	<i>Upgrades</i> due to statistically significantly less grade 3–4 toxicities impacting on daily well-being (Forms 2a and b) <i>Downgrades</i> due to one or more statistically significantly increased incremental toxicities (Form 2b)
<i>Downgrades or upgrades</i> due to positive or negative differences, respectively, of at least 10% in the discontinuation rates (Forms 2a and b)	<i>Not implicated</i>
<i>Downgrades</i> due to no difference in QoL or no QoL assessment performed and only PFS showing an improvement (Form 2b)	<i>Downgrades</i> due to no difference in QoL and only PFS showing an improvement (Form 2b)
<i>Downgrades or upgrades</i> due to statistically significant negative or positive differences (respectively) in QoL (Forms 2a and b)	<i>Upgrades</i> due to statistically significant positive differences in QoL (Forms 2a and b)

Abbreviations: AE, adverse event, CI, confidence interval, HR, hazard ratio, PFS, progression-free survival, QoL, quality of life.

1. Statistically significant OS results.
2. Any applicable statistically significant primary end-point (if 1 does not apply).
3. Any applicable statistically significant secondary end-point (if 1 and 2 do not apply).

Two authors (CW and NG) scored the approval studies by either utilising the original ESMO-MCBS or the adapted ESMO-MCBS. Scoring was also performed by two blinded authors (SW and JDP). Disagreements between scores were reviewed and examined by the scorers (SW, NG and JDP). MCB is defined as scores of 4 or 5 for treatments with palliative intent (on a scale of 1–5) and scores of A or B for therapies with curative intent (on a scale of C to A), as per the original ESMO-MCBS [8].

2.3. Data analysis

Extracted data were compiled into a data form designed in Microsoft Office Excel 2010. We computed the 95% confidence intervals (CIs) of the proportion of therapies meeting the thresholds by bootstrapping with 1,000,000 draws. The calculations of the CIs were conducted in R environment [15].

3. Results

3.1. Characteristics of the approval studies

In total, we identified 70 approval studies (for 38 drugs) that were eligible to apply the original as well as the adapted ESMO-MCBS framework (Table 2 and Table A.4). The most common disease settings were melanoma (21%), lung (21%) and gastrointestinal cancer (17%). In 35 studies (50%), parameters regarding QoL

Table 2

Characteristics of eligible comparative EMA approval studies for solid tumours ($n = 70$).

Characteristics	<i>n</i>	% ^a
Treatment intention		
Palliative	70	100
Indication (ICD-10 category)		
Gastrointestinal cancer (C15–C26)	12	17
Lung cancer (C30–C39)	15	21
Melanoma (C43–C44)	15	21
Sarcoma (C45–C49)	2	3
Breast cancer (C50–C50)	7	10
Cervical carcinoma (C51–C58)	1	1
Ovarian and peritoneal cancer (C51–C58 and C45–C49)	5	7
Prostate cancer (C60–C63)	6	9
Renal cell carcinoma (C64–C68)	4	6
Thyroid carcinoma and neuroendocrine tumour (C73–C75)	3	4
QoL parameter		
Not available	35	50
Available	35	50
Phase of the study		
II	5	7
III	65	93
Statistically significant study end-points		
OS	34	49
PFS	60	86
Other	4	6
Scored end-points		
OS	33	47
PFS	34	49
Other	3	4
Sample size		
Mean	686	
Median	658	
Range	153–1873	

Abbreviations: QoL, quality of life; OS, overall survival; PFS, progression-free survival.

^a Deviation of 100% cumulative percentage may be caused by rounding.

were available. All therapies were palliative in intent. The median sample size was 658. Statistically significant OS and progression-free survival (PFS) results were accessible in 49% and 86% of the studies, respectively.

3.2. Comparison of the two ESMO-MCBS frameworks

Fifteen (21%) of the 70 investigated indications met the threshold for MCB using the original ESMO-MCBS and eight (11%) therapies met MCB threshold using the adapted ESMO-MCBS (Fig. 1). This resulted in 79% (95% CI 68.6–87.1, $n = 55$) of therapies that did not meet the threshold for MCB using the original ESMO-MCBS, of which the majority reached grade 2 ($n = 16$, 23%) and grade 3 ($n = 31$, 44%), while eight (12%) therapies were associated with grades 0 and 1. Eighty nine percent (95% CI 80.0–95.7, $n = 62$) of therapies did not meet the adapted ESMO-MCBS threshold for benefit, which are distributed into the grades 0–3 as follows: 11% ($n = 8$) grade 0, 23% ($n = 16$) grade 1, 31% ($n = 22$) grade 2 and 23% ($n = 16$) grade 3 (Supplementary Table A.1).

With respect to the distribution of all grades, a shift from higher scores to lower scores can be observed when the adapted ESMO-MCBS framework is applied (Fig. 1); grade 3, particularly, was most common in the original ESMO-MCBS compared with grade 2 in the adapted ESMO-MCBS. In addition, an increase of 22% ($n = 16$) in therapies with grades 0 and 1 was observed in the adapted ESMO-MCBS compared with the original framework. As shown in Tables A.2 and A.3, the proportion of drugs meeting MCB thresholds varied across cancers and between ESMO-MCBS frameworks.

4. Discussion

Approximately, 800 drugs and vaccines are currently under investigation in clinical trials for the treatment of cancer. Roughly, 80% of those are first-in-class therapies, and around 73% are intended as personalised and, therefore, targeted medicines [16]. Global costs for anticancer therapies have increased in the last decade, particularly due to targeted agents and immunotherapies [16,17]. On these grounds, and due to the fact that the number of cancer therapies in development is continuing to rise [16], policy-makers and stakeholders are facing potential challenges. In this study, we sought to not only address the clinical benefit of recently EMA-approved cancer drugs, but to also address the potential limitations of the original ESMO-MCBS scale by applying an updated ESMO-MCBS framework to the same cohort of drugs (Table 1 and Table A.4). With respect to the original ESMO-MCBS, 21% of the therapies met the MCB threshold. In contrast, 10% fewer therapies met the threshold for MCB when the adapted ESMO-MCBS was applied, which is not surprising, given the more strict criteria imparted by the adapted framework (Table 1). In both cases, meaningful benefit is lacking in the vast majority of EMA-approved cancer medications over the last 5 years: 89% (95% CI 80.0–95.7) and 79% (95% CI 68.6–87.1) of therapies do not meet the MCB threshold in the adapted and original ESMO-MCBS, respectively—a striking finding, given that on a minority of novel cancer agents are deemed to be clinically meaningful to patients.

The discrepancies between the adapted and original ESMO-MCBS scores (Table 1 and Table A.4) shed light

^aDeviation of 100% cumulative percentage may be caused by rounding.

Fig. 1. Comparison of the original and adapted ESMO-MCBS grades of all EMA-approved drugs for solid tumours (2011–2016).

on areas of potential improvement for the original ESMO-MCBS. The use of the lower CI limit for generating ESMO-MCBS grades not only introduces an optimistic perspective, but also systematically favours drugs with a low certainty in results—a systematic bias that should be avoided in an evidence-based value framework. As in this study, a lowered realisation of the arbitrary benefit threshold when the best estimate of the HR is used has been previously in a different cohort of anticancer agents [9]. The adapted ESMO-MCBS also focuses on any toxicity data presented in the trial, adjusting grades by a threshold percentage difference in experimental and control toxicities in forms a and b (Table 1 and Table A.4), as opposed to only statistically significant toxicity end-points, which are less stringently addressed in forms evaluating OS benefit. Given the overt underscoring of harm that can occur in oncology trials [18], especially in trials with positive primary end-points [19], toxicity burden can be misrepresented at baseline; therefore, any toxicity data presented should be considered. Furthermore, the adapted ESMO-MCBS takes into account the discontinuation rate of the drug under assessment, which is a surrogate for drug intolerance either due to loss of efficacy or increased toxicity, and should be a serious consideration when prescribing oncology medications [20]. For QoL data, both frameworks downgrade one level if a drug only leads to PFS improvement without demonstrating a QoL improvement. However, the adapted ESMO-MCBS also downgrades one level if no QoL assessment was performed, since a paucity of QoL data at the time of scoring should not paradoxically result in a superior grade [13]. This is a moot point in terms of MCB, as the maximum grade obtained for PFS end-points with no QoL improvement by the original ESMO-MCBS would fall below thresholds (i.e. 3); this still may be important, however, when comparing absolute grades between trials. Most importantly, the adapted framework addresses detrimental QoL outcomes in conjunction with OS, resulting in possible downgrading that does not occur in the original ESMO-MCBS. Finally, for the adapted ESMO-MCBS, a one-level downgrade is applied if the median OS is negative when the graded end-point shows a statistically significant, positive difference. Only, in this case, a downgrade of two scores is performed, since OS is the ‘gold standard’ with respect to patient-relevant outcomes and PFS studies often apply cross-over designs that may lead to invalid conclusions about the real benefit of anticancer drugs [21]. Therefore, a negative OS benefit should adjust ESMO-MCBS grades accordingly.

The primary rationale for the proposed adapted ESMO-MCBS was to not only provide a value framework that improves applicability of trial results, but to also provide increased focus on patient-relevant outcomes; the ultimate goal was to generate a grade that may be considered a more accurate reflection of MCB.

The higher weighting of the aforementioned factors avoids the introduction of a systematic bias towards an optimistic perspective that can result in incorrect conclusions and implications when formally assessing MCB. To our knowledge, this is the first study that applies an adapted version of the ESMO-MCBS to a cohort of trials addressing some of the frameworks limitations and comparing framework outputs to the original ESMO-MCBS. Our findings of benefit, focused on EMA-approved therapies and defined by both the original and a less-permissive adapted ESMO-MCBS, are in line with the recently published data. Vivot *et al.*, have shown that many modern Food and Drug Administration (FDA)-approved cancer drugs in the United States (US) do not offer a high clinical benefit using both the ESMO-MCBS and the American Society of Clinical Oncology (ASCO) Value Framework [22]. Kim & Prasad [4] have also focused primarily on 5 years of cancer drugs approved by the FDA, showing that the majority of approved therapies had unknown effects or did not have any improvement in OS; in 67% of instances, approvals were also shown to be the result of surrogate outcomes. In addition, some of our authors have demonstrated that only one-third of anticancer therapies from randomised trials of the last 5 years (notably of which only a minority were FDA-registration trials) meet ESMO-MCBS thresholds for MCB [9].

The major limitation in presenting an adapted ESMO-MCBS framework is its lack of validation, which is a pertinent strength of the original ESMO-MCBS: it has been externally validated against results with those of health technology assessments carried out across Europe, showing agreement [23]. The original incarnation of the ESMO-MCBS has been heavily peer-reviewed for reasonableness, while the adapted has not. Our goal was, therefore, not to replace the original ESMO-MCBS, but, rather, further the discussion on objectifying clinical benefit, as well as provide ‘real world’ examples of anticancer agents scored against a stricter outlook on benefit (Table A.4). In addition, we used several exclusion criteria (Fig. A.1) that may lead to a bias and trend towards more positive results, especially since studies with non-statistically significant data and single-arm studies were not considered. We also did not address protracted survival benefit that may be imparted by therapies providing a durable response, as is explicitly, and importantly, addressed in the ASCO Value Framework [24]; this should be a consideration in future iterations of the ESMO-MCBS. Finally, as in the original ESMO-MCBS, the adapted framework does not explicitly consider cost, which is an important factor in decision making, especially since the prices for anticancer treatments are rising [17]. Since comparable frameworks simply ‘drop’ the cost of the therapy as the final input into the framework analysis [24], in a similar vein, costs can be considered by the ESMO-MCBS once a grade is established.

Our results, in combination with other recently published analyses, demonstrate that the threshold for MCB is not met by the majority of EMA-approved cancer drugs, with limited evidence on the clinical benefit available at the time of approval in approximately half of the study cohort. Hence, an approval status of an oncology drug may not confer a relevant health benefit for patients. In addition, approvals on the basis of a paucity of evidence are bound to increase due to new fast-track approval pathways, which is already a focus of criticism in the US [1–3]. Therefore, stakeholders and decision makers need to continually assess the benefit-risk ratio of new cancer drugs to ensure a balanced and an equitable distribution of resources in our health care systems. In doing so, ESMO-MCBS provides an opportunity to predict the MCB of oncology drugs in a standardised way. Future iterations of the ESMO-MCBS will need to incorporate additional cost-effectiveness analyses that will be necessary to not only determine the MCB of novel drugs, but to support the allocative decisions on our scarce health care resources.

Conflict of interest statement

None declared.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.ejca.2017.05.029>.

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