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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.

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: