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Magnitude of Clinical Benefit of Cancer Drugs Approved by the US Food and Drug Administration

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Abstract

Background: It is uncertain whether drugs approved by the US Food and Drug Administration (FDA) have clinically meaningful benefit as determined by validated scales such as the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS).

Methods: We searched the Drugs@FDA website for applications of anticancer drugs from January 2006 to December 2016. Study characteristics, outcomes, and regulatory pathways were collected from drug labels and reports of registration trials. For randomized controlled trials (RCTs), ESMO-MCBS grades were applied. Meaningful benefit was defined as a grade of A or B for (neo)adjuvant intent and 4 or 5 for palliative intent. All statistical tests were two-sided.

Results: We identified 63 individual drugs for 118 indications. These were supported by 135 studies, among which were 105 RCTs for which ESMO-MCBS could be applied. Only 46 (43.8%) met the ESMO-MCBS meaningful benefit threshold (100% of (neo)adjuvant trials and 38.8% of palliative trials). In palliative therapy trials, meaningful ESMO-MCBS grades were associated with phase III trials (compared with phase II; odds ratio [OR] = 38.45, 95% confidence interval [CI] = 3.27 to 452.00, $P = .004$), those with overall survival as their primary end point (compared with intermediate end points; OR = 8.28, 95% CI = 2.49 to 27.50, $P = .001$) and trials of targeted drugs with companion diagnostics (OR = 11.62, 95% CI = 2.95 to 45.78, $P < .001$). Over time, there has been an increase in the number of trials meeting the ESMO-MCBS threshold ($P_{trend} = .04$). There were insufficient (neo)adjuvant studies to perform statistical analysis.

Conclusions: The number of trials meeting the ESMO-MCBS threshold for clinical benefit has improved over time. However, fewer than half of RCTs supporting FDA approval meet the threshold for clinically meaningful benefit.

The US Food and Drug Administration (FDA) criteria for drug approval require substantial evidence of clinical benefit from adequate and well-controlled trials (1). Efficacy should be demonstrated by either prolonging patient survival or improving quality of life (QoL), or both. There is ongoing controversy over the FDA's current drug approval mechanisms (2–4). While the FDA's statutory mandate does not provide a provision for the exception of drugs used by selected subgroups such as terminally ill patients, the last 40 years have shown a relative softening of rules for anticancer drugs (5), including the use of accelerated approvals. Additionally, regulations aimed at speeding up the review process (fast track, priority review, and breakthrough therapy designations) (6–8), as well as orphan drug designations (9), have been promoted to improve access to

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therapeutics for life-threatening diseases, including cancer. The benefits of the current system of rapid review and approval are uncertain. Shortened development and review times and earlier marketing of drugs have been associated with negative outcomes (10,11) and have raised questions about the rigor and safety of data supporting regulatory approval (12–14).

There are concerns that advances in cancer therapy provide limited meaningful benefit to patients (15,16). In response, oncology societies have attempted to provide a standardized approach to grading clinical benefit. While some had the principal aim of providing structure for reimbursement decisions by payers (17–19), others were initiated in order to encourage patients and investigators to demand more from clinical trials (20). Among these, the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) is a validated and reproducible tool used to assess the magnitude of clinical benefit for drugs for the treatment of solid tumors (17,18). Although initially motivated by the inconsistency in access to cancer drugs among economically diverse European countries, it has been used as a tool for the assessment of benefit from anticancer drugs studied in unselected clinical trials (21,22). Additionally, in contrast to other scales, it provides a threshold for the determination of clinical benefit rather than providing an ordinal scale for the assessment thereof.

Despite the above data, the consistency of evidentiary standards used by the FDA for drug approval and those considered clinically meaningful by oncology professional societies is uncertain. Here, we evaluate characteristics and outcomes of clinical trials supporting approval by the FDA and their association with ESMO-MCBS. Also, we explore the association between the ESMO-MCBS thresholds for meaningful clinical benefit and both different regulatory pathways and orphan drug designations.

Methods

Data Sources

We searched the Drugs@FDA website (23) to identify applications of anticancer drugs between January 2006 and December 2016. Initially, we identified all approved anticancer drugs and then excluded drugs approved for hematologic malignancies or for pediatric populations. We also excluded supportive care drugs and nontherapeutic agents, such as medical devices.

Data Extraction

Data were extracted by two authors (AT and CM) using predesigned electronic forms. Disagreement was resolved by consultation with a third author (EA). Data extraction was conducted between October 2016 and December 2016.

The following characteristics were collected for each application: submission type (initial indications vs supplemental indications) and type of application (New Drug Application or Biologic Licensing Application), regulatory pathways, including both type of review (fast track [24], priority or standard review [25,26], breakthrough or nonbreakthrough therapy [27], and orphan or nonorphan designation [28], as determined by the FDA) and type of approval (accelerated or regular approval [29]). We also collected data on whether a companion diagnostic test was available, as defined by the FDA framework (30).

Drug labels (31) were reviewed to identify the meeting date, drug name, and data on number of trials supporting the application. When more than one study supported a single application, each trial was considered separately. Clinical trial information, including number of trials supporting the indication (single trial vs more than one trial), trial sample size, trial design (randomized vs single arm), blinding (blinded vs open-label), phase of clinical trial (phase I–II vs phase III), treatment intent ([neo]adjuvant vs palliative], primary efficacy end points supporting the application (overall survival vs intermediate end points [eg, progression-free survival or tumor response rate]), whether crossover was allowed (or not), whether or not approval was based on a subgroup analysis of the pivotal trial, and whether the drug was a "me-too" compound (defined as a drug that is structurally very similar to other drugs already approved for the same indication [cancer site and line of therapy]). For studies with coprimary end points, we identified the most definitive primary end point chosen by FDA to support approval, preferring end points such as overall survival to intermediate end points such as disease-free or progression-free survival. For trials performed in the palliative setting, we also collected data on line of therapy (first line vs other). Finally, the application number was collected to cross-reference with the drug label (31).

Data Synthesis and Scoring

For randomized controlled trials (RCTs), ESMO-MCBS grades were applied by two authors (AT and CM). Data on efficacy, safety, and QoL were collected using the appropriate ESMO-MCBS form (17,18). Drug labels and reports of trials supporting registration were utilized, and the ESMO-MCBS grade was assigned based on the lower limit of the 95% confidence interval (CI) of the hazard ratio (HR), and in conjunction with the minimum absolute gain in outcome. Studies with preplanned subgroup analyses with a maximum of three subgroups could be graded. When statistically significant results were reported for more than one subgroup, then each subgroup was evaluated separately and assigned a separate grade. Studies and subgroups not showing statistically significant results were not graded (17,18). Only statistically significant changes in toxicity or QoL were used to modify ESMO-MCBS grades. Meaningful clinical benefit was deemed to be a grade of A or B for trials of (neo)adjuvant intent and 5 or 4 for those of palliative intent. These cutoffs have been shown to be valid and reproducible regardless of the evaluation form utilized for data collection (17,18).

Statistical Analysis

Data were reported descriptively as proportions, medians, and ranges where appropriate. Comparisons between groups were assessed using the Mann-Whitney *U* test and chi-square tests for continuous and categorical variables, respectively. Trends over time were assessed using linear regression. Associations between characteristics of trials and approval pathways and ESMO-MCBS clinically significant benefit grades were explored using logistic regression and reported as odds ratios (ORs) and their respective 95% confidence intervals (CIs). Analyses were conducted initially in the univariate setting. All variables with a *P* value of less than .10 were then included in a multivariable analysis. Collinearity was assessed using the variable inflation factor and tolerance statistics. Three sensitivity analyses were performed. First, we excluded applications for which more than one trial was used to support approval or for which approval was based on a subgroup analysis, thereby focusing only on

pivotal trials supporting registration. Second, we excluded me-too drugs, defined as products that largely duplicate the actions of existing approved drugs. Finally, to assess the sensitivity of the lower limit of the 95% confidence interval, we performed a post hoc sensitivity analysis in which we used the estimate of the hazard ratio rather than the 95% confidence interval to calculate the ESMO-MCBS. Data analyses were conducted using SPSS version 21 (IBM Corp, Armonk, NY). All statistical tests were two-sided, and statistical significance was defined as a two-sided P value of less than .05. No corrections were made for multiple testing.

Results

Drugs Approved

Between January 1, 2006, and December 31, 2016, the FDA approved 63 individual drugs for 118 solid tumor indications. Characteristics of approved applications are shown in Table 1. Included applications were supported by 135 individual trials (128 pivotal trials and seven supportive trials). Among the 135 included trials, four studies included multiple subgroups suitable for analysis. Consequently, a total of 139 data points were available for analysis, 109 (78.4%) of which were derived from RCTs. Characteristics of trials supporting drug approval are shown in Table 2. Details of included drugs, their approval pathways, and the design of the trials supporting registration are shown in Supplementary Table 1 (available online).

Table 1. Characteristics of included applications

Characteristics	No. (%)
Applications	118 (100)
Type of application	
New drug application	72 (61.0)
Biologic licensing application	46 (39.0)
Type of indication	
Initial	51(43.2)
Supplemental	67 (56.8)
Type of approval	
Regular	91 (77.1)
Accelerated	27 (22.9)
Orphan drug designated approvals	
Yes	54 (45.8)
No	64 (54.2)
Priority review	
Yes	92 (78.0)
No	26 (22.0)
Number of trials supporting approval	
1	97 (82.2)
>1	21 (17.8)
Decision based on	
Subgroup analysis	15 (12.7)
Entire study population	103 (87.3)
Breakthrough therapy designation*	
Yes	22 (18.6)
No	46 (39.0)

*Breakthrough therapy designation came into effect in July 2012.

Regulatory Pathways and Orphan Drug Designation

Of the 118 applications, 92 (78.0%) were granted priority review. Twenty-seven (22.9%) applications received accelerated approval, and these were supported by 33 trials, 17 (51.5%) of which were single-arm studies. Fifty-four applications (45.8%) were given orphan designation and were supported by 66 studies. Among these, 18 (27.3%) were single-arm studies. A total of 68 applications were approved after the FDA Safety and Innovation Act came into effect in July 2012, thereby allowing for breakthrough therapy designation. Among these, 22 (32.4%) drugs were approved as breakthrough therapies. Table 3 shows characteristics of trials and approval pathways for orphan and nonorphan drugs. Compared with nonorphan drugs, trials supporting orphan drug approval had a smaller sample size, were less likely to evaluate experimental cytotoxic chemotherapy or endocrine therapy than targeted therapy, were less often randomized, and were more likely to assess intermediate end points rather than overall survival.

ESMO-MCBS Thresholds

ESMO-MCBS could not be applied to the 28 single-arm studies included in the analytical cohort. Of the included 109 RCTs, two trials included multiple subgroups suitable for analysis, resulting in 111 data points available for scoring for ESMO-MCBS. Of these, ESMO-MCBS was successfully applied to 105 data points (94.6%). Of those data points for which ESMO-MCBS could not be applied, in three cases (2.7%) the experimental drug was included in both arms, and in another three cases (2.7%) the primary end points were not suitable for assessment (one evaluated the safety and tolerability with neoadjuvant treatment, one used pathological complete response with neoadjuvant therapy, and one used biochemical surrogate end points).

Details of the analyzed RCTs and the scores derived from the ESMO-MCBS are provided in Supplementary Table 2 (available online). Of these, seven (6.7%) were in the (neo)adjuvant setting and 98 (93.3%) in the palliative setting. Only 46 (43.8%) met the ESMO-MCBS clinically meaningful benefit threshold (100% of (neo)adjuvant trials and 38.8% of palliative trials). This included 45.6% of drugs receiving regular approval and 18.5% of those receiving accelerated approval. In a sensitivity analysis in which the hazard ratio rather than lower 95% confidence interval was used to calculate the ESMO-MCBS, scores were changed for 16 studies (15.2%). These comprised 13 trials performed in the palliative setting and three in the (neo)adjuvant setting). Among these, clinically meaningful ESMO-MCBS scores were changed in only three cases (2.9% of all analyzed RCTs). Similar data were observed when focusing only on pivotal trials and excluding data from supportive trials; 44 of 101 pivotal trials (43.6%) met clinically meaningful thresholds. Similarly, when including only the highest ESMO-MCBS score from any trial supporting approval (n = 96 data points), 10 (42.7%) met clinically meaningful thresholds.

Over time, there has been an increase in the number of trials meeting the ESMO-MCBS threshold (33.2% in 2006 vs 66.8% in 2016, $P_{trend} = .04$), with most of the effect occurring between 2011 and 2016 (see Figure 1). After excluding me-too drugs, the magnitude of effect was maintained, but statistical significance was lost (number of trials meeting the ESMO-MCBS threshold was 9.5% in 2006 vs 50.0% in 2016, $P = .14$). This effect seemed to be influenced by more frequent observation of improved QoL or reduced toxicity in later years ($P_{trend} = .03$). There was no apparent improvement in relative efficacy over time (HR for overall survival $P_{trend} = .68$, HR for intermediate end points $P_{trend} = .37$).

Table 4 shows association between clinically meaningful ESMO-MCBS grades and trial- and approval-related

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Table 2. Characteristics of trials supporting drug approval

Characteristics	No. (%)
Studies available	139 (100)*
Sample size	
Median	528
Range	12–3752
Tumor type	
Lung cancer	30 (21.6)
Breast cancer	14 (10.1)
Colon cancer	11 (7.9)
Prostate cancer	4 (2.9)
Other	78 (56.1)
Companion diagnostic test†	
Yes	34 (24.5)
No	105 (75.5)
Study design	
Randomized	111 (79.9)‡
Single arm	28 (20.1)
Phase of study	
I	6 (4.3)
I/II	3 (2.2)
II	33 (23.7)
II–III	2 (1.4)
III	95 (68.3)
Blinding	
Open-label	96 (69.1)
Double-blind	43 (30.9)
Time-to-event as primary end point	
Yes	100 (71.9)
No	39 (28.1)
Primary end point	
Overall survival	55 (39.6)
Intermediate end point	84 (60.4)
Quality of life data	
Improvement	21 (15.1)
No improvement	24 (17.3)
Not reported	92 (66.2)
Analysis ongoing	2 (1.4)
Experimental drug	
Cytotoxic chemotherapy	19 (13.7)
Endocrine therapy	3 (2.2)
Immunotherapy	25 (18.0)
Therapeutic antibody	31 (22.3)
Small molecule	55 (39.6)
Other	6 (4.3)
Me-too drug	
Yes	29 (20.9)
No	110 (79.1)

*This cohort included 135 trials, four of which reported statistically significant preplanned subgroup analyses used to support approval that were evaluated independently. This resulted in a total of 139 data points.
†Classification of a drug as having a companion diagnostic test was determined by the US Food and Drug Administration (30).
‡Includes 109 individual randomized trials, two of which reported statistically significant preplanned subgroup analyses used to support approval that were evaluated independently. This resulted in 111 data points.

Table 3. Characteristics of trials based on orphan drug designation

Variable	Orphan drugs (n = 66) No. (%)	Nonorphan drugs (n = 73) No. (%)	P*
Cancer sites			<.001
Lung	13 (19.7)	17 (23.3)	
Breast	0 (0)	13 (17.8)	
Colorectal	0 (0)	11 (15.1)	
Prostate	0 (0)	6 (8.2)	
Other	53 (80.3)	26 (35.6)	
Experimental drug type			.005
Cytotoxic chemotherapy	4 (6.1)	13 (17.8)	
Endocrine therapy	1 (1.5)	2 (2.7)	
Immunotherapy	11 (16.7)	13 (17.8)	
Therapeutic antibody	12 (18.2)	18 (24.7)	
Small molecule	32 (48.5)	21 (28.8)	
Other	6 (9.1)	6 (8.2)	
Median sample size (range)	369 (28–1093)	687 (12–1725)	.001
Approval based on subgroup analysis	11 (16.7)	11 (15.1)	.80
Breakthrough therapy designation	14 (21.2)	14 (19.2)	.45
Priority review	54 (81.8)	55 (75.3)	.36
Accelerated approval	19 (28.8)	13 (17.8)	.13
Initial approval (vs supplemental)	31 (47.0)	30 (41.1)	.57
Multiple trials supporting approval	23 (34.8)	17 (23.3)	.19
Randomized trials	48 (72.7)	63 (86.3)	.047
Phase III	42 (63.6)	52 (71.2)	.22
Blinding	20 (30.3)	23 (31.5)	.83
Firstline	20 (30.3)	21 (28.8)	.92
Companion diagnostic	19 (28.8)	12 (16.4)	.10
Intermediate end point	47 (71.2)	37 (50.7)	.01
First in class†	10 (34.5)	2 (2.7)	.08

*Based on Mann-Whitney *U* test and chi-square tests for continuous and categorical variables, respectively. All *P* values are two-sided.
†This classification was only available for applications after 2011 (29 orphan drug approvals and 18 nonorphan drug approvals)

characteristics for drugs used in the palliative setting. In univariable analysis, there were higher odds of clinically meaningful grades in trials supporting regular approval (compared with accelerated approval), phase III trials (compared with randomized phase II trials), those with higher sample sizes, those with overall survival as their primary end point (compared with intermediate end points), and trials of targeted drugs with companion diagnostics. There was no evidence of substantial collinearity among statistically significant variables in univariable analysis (data not shown). In multivariable analysis, statistical significance was maintained for phase III trials (compared with phase II trials; OR = 38.45, 95% CI = 3.27 to 452.00, $P = .004$), those with overall survival as their primary end point (compared with intermediate end points; OR = 8.28, 95% CI = 2.49 to 27.50, $P = .001$), and trials of targeted drugs with companion diagnostics (OR = 11.62, 95% CI = 2.95 to 45.78, $P < .001$). However, statistical significance was lost for trials supporting regular approval (compared with accelerated approval) and those with higher sample sizes (Table 4). There was an insufficient number of (neo)adjuvant studies to perform statistical analysis in this setting.

In a sensitivity analysis excluding data points that were based on supportive trials and subgroup analyses (ie, including only pivotal trials), similar results were observed, other than the loss of statistically significant association between companion diagnostics and clinically meaningful ESMO-MCBS grades (see Supplementary Table 3, available online). Additionally, the magnitude of effect of phase III trials was smaller, but it retained statistical significance.

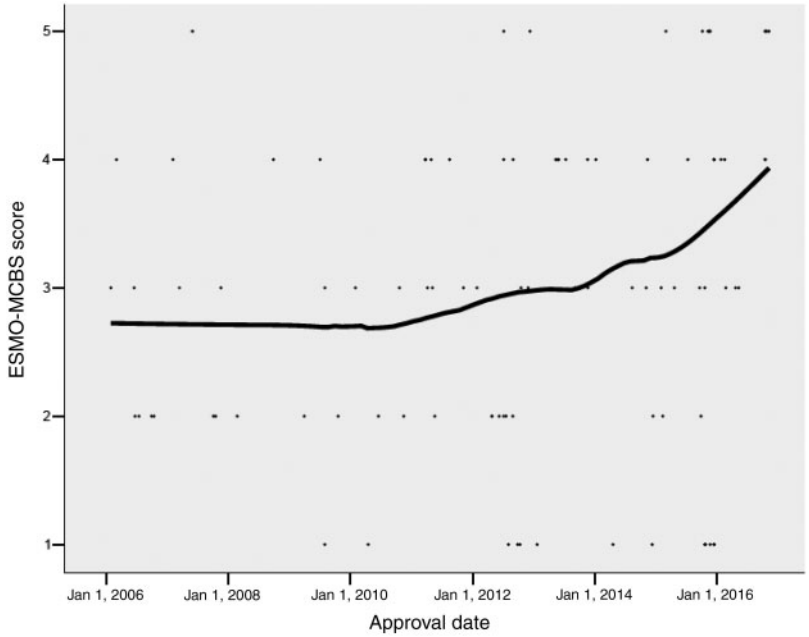

Figure 1. European Society for Medical Oncology Magnitude of Clinical Benefit Scale clinically meaningful scores among trials supporting US Food and Drug Administration drug approvals over time. Trends over time were evaluated with locally weighted scatterplot smoothing. ESMO-MCBS = European Society for Medical Oncology Magnitude of Clinical Benefit Scale.

Table 4. Associations with ESMO-MCBS clinically meaningful scores*

Variable	OR (95% CI)	P†
Univariable analysis		
Sample size	1.00 (1.00 to 1.01)	.02
Multiple trials supporting approval (vs one trial)	1.43 (0.71 to 2.90)	.32
Phase III (vs not)	25.79 (3.39 to 196.00)	.002
Overall survival (vs intermediate end point)	8.00 (3.41 to 18.76)	<.001
Blinded trial (vs open label)	1.80 (0.85 to 3.80)	.12
Companion diagnostic (vs none)	3.05 (0.132 to 7.06)	.01
Firstline (vs later lines)	1.80 (0.85 to 3.80)	.12
Crossover (vs not)	0.85 (0.36 to 2.01)	.70
Regular approval (vs accelerated approval)	3.52 (1.14 to 10.88)	.03
Breakthrough therapy designation (vs not)	1.29 (0.50 to 3.37)	.60
Priority review (vs not)	1.18 (0.48 to 2.95)	.72
Fast track (vs not)	1.34 (0.52 to 3.48)	.55
Me-too drug (vs not)	1.46 (0.60 to 3.52)	.41
Orphan drug designation (vs not)	1.03 (0.49 to 2.18)	.93
Multivariable analysis		
Sample size	1.00 (0.99 to 1.00)	.26
Phase III (vs not)	38.45 (3.27 to 452.00)	.004
Overall survival (vs intermediate end point)	8.28 (2.49 to 27.50)	.001
Companion diagnostic (vs none)	11.62 (2.95 to 45.78)	<.001
Regular approval (vs accelerated approval)	1.54 (0.32 to 7.35)	.59

*This analysis included 98 randomized trials in the palliative setting. CI = confidence interval; ESMO-MCBS = European Society for Medical Oncology Magnitude of Clinical Benefit Scale; OR = odds ratio.
†Based on logistic regression. All P values are two-sided.

Discussion

Decisions to prescribe drugs based on labeled indications are associated at least in part with the expectation that regulatory agencies have assessed safety and efficacy and that these have met acceptable thresholds (4). Although oncology societies and other professional organizations are increasingly recognizing the importance of establishing clinically meaningful thresholds for cancer therapies (17,18,20,21), little is known about whether thresholds used by regulators are similar to those accepted by clinicians (32–35). In the current study, we applied systematically the ESMO-MCBS to RCTs supporting FDA drug approval over the last decade. We analyzed both first and supplemental indications of drugs and evaluated the clinical benefit based on data submitted for approval. Results show that only 43.8% of RCTs meet the threshold for meaningful benefit, perhaps reflecting the previously described softening of the FDA's evidentiary standards for cancer drugs.

Despite this finding, our analysis demonstrates a number of encouraging results. First, there has been an increase in the number of trials meeting the arbitrary ESMO-MCBS threshold over time. This observation appears to have been influenced by an increase in trials showing improved QoL or improvement in safety profile over time. This may relate to the increasing number of approvals for immunotherapy and drugs with companion diagnostics in recent years (36). Typically, such treatments have shown both improvements in efficacy and either an improvement in QoL or a reduction in drug-related toxicity, thereby resulting in higher ESMO-MCBS scores (37). Second, RCTs of curative-intent therapy are more likely than palliative-intent trials to meet ESMO-MCBS criteria for meaningful benefit. These results are consistent with previous work evaluating ESMO-MCBS thresholds in a larger cohort of RCTs, including those not used in support of drug approval (22); however, they are slightly higher that a more limited assessment of FDA drug approvals reported previously (35). This small difference could be

explained by sampling bias. Vivot and colleagues explored only RCTs for 51 new drugs approved by the FDA between 2000 and 2015, and we analyzed a more comprehensive cohort of 135 trials.

Of interest, our study shows that drugs approved with a companion diagnostic test were more likely to meet ESMO-MCBS thresholds. In recent years, a new understanding of the molecular basis of cancer has resulted in the successful development of new drugs (38–42). This, in turn, has created a demand for flexibility in clinical trial design, rapid drug approval, and early access to new drugs (3). In this study, trials supporting rapid review (fast track, priority review, breakthrough therapy) or approval (accelerated approval) were associated with similar ESMO-MCBS grades as those approved through regular review and approval pathways. However, phase III trials, as well as those with overall survival as their primary end point, were associated independently with higher ESMO-MCBS grades, suggesting that RCTs powered for definitive (rather than intermediate or surrogate end points) can provide a sound basis for establishing the utility of cancer drugs (43). Of interest, more than half of studies supporting accelerated approvals were based on single-arm studies for which ESMO-MCBS could not be calculated. Exclusion of drugs tested in noncomparative trials may have resulted in drugs approved through accelerated pathways having aberrantly low ESMO-MCBS scores, with a lower proportion meeting clinically meaningful thresholds. All drugs approved through accelerated pathways are mandated to have confirmatory studies in order to establish the effect of drugs, especially if approval is based on noncomparative studies.

Our study shows that almost half of drug approvals for solid cancers receive orphan drug designations. In addition, compared with nonorphan drugs, trials supporting orphan drug approvals were more likely to be smaller, to use single-arm trial design, and to assess intermediate efficacy end points. These results are consistent with the findings of Kesselheim et al. (13), who studied this question in a smaller cohort of 15 orphan and 12 nonorphan drugs approved between 2010 and 2014. In our study, there was no apparent difference in the odds of clinically meaningful ESMO-MCBS grades among drugs with orphan designations than those without. In addition, studies leading to orphan drug approvals were less likely to use chemotherapy or endocrine therapy and more likely to evaluate a variety of new targeted therapies (including immunotherapy), suggesting that the orphan drug incentives encourage drug innovation in this field. Finally, a substantial proportion of studies approved with orphan drug designation are in lung cancer, suggesting that the Orphan Drug Act encourages sponsors to divide common conditions into rare subgroups in which existing therapies are limited (44).

Despite validation and field testing, the ESMO-MCBS grading system and its constructs of clinical benefit have not been accepted universally. A common criticism is the use of the lower 95% confidence interval to assess for efficacy benefit rather than the estimate of the hazard ratio. To address this, we performed a sensitivity analysis in which we utilized the hazard ratio rather than the lower 95% confidence interval to calculate the ESMO-MCBS scores. Results show that scores were changed in fewer than one in six studies, with clinically meaningful thresholds changing in only 2.9% of cases. The main reason for this is that ESMO-MCBS scores for noncurative therapies with a primary end point of overall survival were more commonly determined by the difference in absolute survival at two or three years rather than by the relative effect on survival (measured as the hazard ratio or its lower 95% confidence interval).

Our study has limitations. First, although efficacy end points were collected from FDA labels, grade 3 and 4 toxicities and QoL data were extracted from published articles. Unfortunately, QoL information was missing frequently from drug labels, and toxicity information was reported often as a pooled analysis based on data derived from multiple trials. This made consistent grading of clinical trials challenging. Second, the analysis of clinical benefit can change over time. Specifically, some drugs are approved based on studies without mature survival data, and once mature survival data become available, the ESMO-MCBS grade may change. Similarly, toxicity data reported initially may be incomplete; reporting of new adverse events after longer follow-up has been described in the literature (45). Third, many studies in our cohort were single arm (20.1%), which limits the applicability of ESMO-MCBS. It is expected than the grading of single-arm data will be incorporated into the next version of the ESMO-MCBS (19). Fourth, caution should be taken when generalizing results obtained applying the ESMO-MCBS framework for drugs approved at a period of time prior to the development of the scale. Finally, in light of the historic association of softer FDA criteria toward drugs used in terminal illness (5) and the validation of the ESMO-MCBS in cancer trials only, these data are not generalizable to noncancer settings.

In summary, in patients with advanced solid tumors, an increasing number of approved drugs meet the ESMO-MCBS threshold for clinical benefit. However, fewer than half of RCTs supporting FDA approval meet the threshold for clinically meaningful benefit. The oncology community must continue to demand high standards for cancer clinical trials and prioritize therapies with clinically meaningful outcomes.

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