



Use of the ESMO-Magnitude of Clinical Benefit Scale to guide HTA recommendations on coverage and reimbursement for cancer medicines: a retrospective analysis



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Summary

Background Recommendations by countries' health technology assessment (HTA) agencies are used to decide which new therapies warrant the allocation of limited health-care resources to make them available through publicly funded health systems. This process is of public health importance for balancing the dual aims of optimising patient outcomes while ensuring financial sustainability. We evaluated which factors affect HTA outcomes and the time to positive HTA outcome, focussing on the role of clinical benefit evaluated with the European Society for Medical Oncology-Magnitude of Clinical Benefit Scale (ESMO-MCBS).

Methods In this retrospective analysis, data were extracted from publicly available HTA reports and related sources from six country settings and their respective HTA agencies (Australia, Canada, England, France, the Canadian province of Quebec, and Scotland). We evaluated new cancer medicines for treating solid tumours in a non-curative setting with published ESMO-MCBS scores and that had been assessed by at least three HTA agencies between Jan 1, 2011, and Dec 31, 2020. Using ESMO-MCBS score as an independent variable, we did descriptive and multivariable regression analyses to evaluate: (1) factors associated with the time between marketing authorisation and positive (unrestricted [List] and restricted [List with Constraints]) HTA outcome; and (2) factors associated with HTA outcomes.

Findings 67 medicine–indication pairs used in non-curative settings were identified, totalling 360 HTA submissions (medicine–indication–country triplets) reviewed by the six HTA agencies. Factors significantly associated with a reduced interval between marketing authorisation and a positive (unrestricted or restricted) HTA outcome included a high ESMO-MCBS score (ie, 4 or 5, vs a low or average score of 1–3; hazard ratio [HR] per 1 month increment 1.42 [95% CI 1.11–1.81], $p=0.0055$), parallel review (vs standard marketing authorisation process; HR 1.69 [1.13–2.54], $p=0.011$), having a risk-sharing agreement or special funding arrangements (vs no funding agreement, HR 4.62 [95% CI 2.51–8.51], $p<0.0001$, and HR 4.16 [2.03–8.50], $p=0.0001$, respectively), and assessment by particular HTA agencies (pan-Canadian Oncology Drug Review vs National Institute for Health and Care Excellence [NICE], HR 2.82 [1.68–4.75], $p=0.0001$; and Haute Autorité de Santé vs NICE, HR 5.70 [2.87–11.33], $p<0.0001$). Accelerated marketing authorisation was significantly associated with a longer time to positive HTA outcome (vs standard authorisation process; HR 0.70 [95% CI 0.51–0.95], $p=0.024$). Positive HTA outcomes (both unrestricted and restricted) were significantly associated with a high ESMO-MCBS score (vs low or average ESMO-MCBS score; relative risk ratio [RRR] 14.10 [95% CI 3.54–56.20], $p=0.0002$, and RRR 4.52 [1.90–10.75], $p=0.0006$, respectively) and acknowledgment of unmet medical need (vs unmet need not recorded, RRR 22.73 [5.51–93.73], $p<0.0001$, and RRR 1.87 [1.18–2.97], $p=0.0075$, respectively). By contrast, positive HTA outcomes (unrestricted and restricted) were inversely associated with uncertainties regarding inputs to economic models informing HTA submissions (vs uncertainties not recorded, RRR 0.28 [0.10–0.78], $p=0.014$, and RRR 0.45 [0.25–0.82], $p=0.010$, respectively). Regarding country-relevant effects, inverse associations with positive HTA outcomes (both unrestricted and restricted) were observed for assessment in Quebec (vs England; RRR 1.15×10^{-6} [1.44×10^{-7} – 9.09×10^{-6}], $p<0.0001$, and RRR 0.33 (0.24–0.46), $p<0.0001$, respectively) and for assessment in Australia (vs England; RRR 1.78×10^{-6} [1.04×10^{-8} – 3.00×10^{-4}], $p<0.0001$, and RRR 0.30 [0.15–0.61], $p=0.0008$, respectively).

Interpretation Several factors informed HTA outcomes for new cancer medicines. A high ESMO-MCBS score, defined as indicating substantial clinical benefit, increased the likelihood of a positive HTA outcome and shortened the interval between marketing authorisation and HTA outcome, and this association was not affected by other variables. Additional factors informing HTA outcomes include evidence uncertainties and unmet medical need. Country-relevant differences exist in the time-to-HTA outcome and the propensity of some countries to achieve positive (restricted or unrestricted) outcomes compared with others.

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Research in context

Evidence before this study

Value frameworks have been developed in recent years as decision-support tools in several contexts; one of these contexts is to inform coverage decisions by health insurers and health technology assessment (HTA) agencies. Many value frameworks focus on cancer therapies, including the European Society for Medical Oncology-Magnitude of Clinical Benefit Scale (ESMO-MCBS). A literature search was done of PubMed, ProQuest, Web of Science, Cumulative Index to Nursing and Allied Health Literature, and EconLit between Jan 1, 2010, and Dec 31, 2023, to identify sources relating to the use of value frameworks as decision support systems in the context of HTAs and in informing coverage decisions for new cancer medicines. The search terms included combinations of ["HTA" OR "health technology assessment*"], ["ESMO-MCBS" OR "ESMO" OR "MCBS" OR "magnitude of clinical benefit scale*" OR "clinical benefit*"], and ["oncol*" OR "cancer" OR "pharmaceutical*"], and the search was limited to articles in the English language. Evidence suggests that the recommendations of HTA agencies are influenced primarily by a new therapy's clinical benefit and price, its impact on the budget, and several other product-specific and disease-specific characteristics that reflect additional value features, which might differ among countries. Differences in how evidence is interpreted and in how contextual factors are considered can reflect differences in value judgments across settings. Some of these differences in evidence interpretation might be due to an absence of robust data regarding the clinical benefit of new cancer medicines available at the time they receive marketing authorisation, thereby confounding the ability of HTA agencies to evaluate key benefit dimensions.

Added value of this study

This study used a custom-built dataset to identify parameters of benefit associated with final HTA outcomes, and the speed at which outcomes were reached, in six high-income countries that use different approaches to HTA. We examined whether the ESMO-MCBS score can be used to predict HTA outcomes, and the time to positive outcome, and controlled for a range of

variables that had not been considered in previous studies, including clinical and economic uncertainties and considerations beyond costs and clinical effects (eg, unmet medical need, administration advantage, and disease severity). Our empirical investigation found that a high ESMO-MCBS score (ie, 4 or 5), as a measure of substantial clinical benefit as defined by ESMO, is a significant predictor of positive HTA outcomes. Several other factors were shown to be significantly associated with positive HTA outcomes, notably orphan designation, having an active comparator in the clinical trial of the medicine–indication, having a double-blind study design, and unmet medical need. We accounted for the effect of clinical and economic uncertainties on the final HTA outcome and found that uncertainties relating to inputs to economic model informing submissions to HTA agencies, in terms of utilities and costs, are negatively associated with HTA outcomes. Additionally, uncertainties over the magnitude of clinical benefit showed a negative association with HTA outcomes. Finally, our model captured differences at the country level and over time. Overall, our model identified factors that can lead to positive HTA outcomes and reimbursement by health systems, and how various factors affect the time it takes for HTA outcomes to be reached.

Implications of all the available evidence

Our model identified critical parameters in value assessments that shape the reimbursement of cancer medicines in a range of high-income countries that use different HTA approaches. Our analysis provides support for the validity of the ESMO-MCBS score as a measure of clinical benefit and highlights its value as part of the HTA decision making process for cancer medicines. Unmet medical need was identified as a positive decision modifier, whereas uncertainties regarding the robustness of clinical and economic evidence adversely affected HTA outcomes. Natural extensions of this study include the analysis of haematological malignancies, cancer medicines designed for curative treatment, and HTA decision making for cancer medicines in upper-middle income countries.

Introduction

In recent years, many new cancer medicines have been approved, and, once approved, these medicines are often marketed at increasingly higher prices; consequently, oncology is now considered the most expensive therapeutic field.^{1–3} However, all new cancer medicines are not equally valuable, as many new medicines provide only a marginal added clinical benefit to patients. A common criticism is that new cancer medicines are not priced relative to their value.^{4–6} Given the constrained budgets of publicly funded health systems, prioritising the allocation of limited financial resources with respect to new therapies is becoming increasingly important; in many countries, this process

is done by the respective health technology assessment (HTA) agency.⁷

In publicly funded health systems, the time interval between receiving marketing authorisation from the regulatory authority and patients' access to the new medicine is ascertained largely by the time it takes the HTA agency to recommend that a new product be reimbursed.⁸ In general, HTA outcomes are influenced primarily by new therapies' clinical benefit and price,⁹ impact on the budget, and several product-specific, disease-specific, and context-specific characteristics that reflect additional value features.¹⁰ These features can differ among countries¹¹ and, even with use of the same evidence base, HTA outcomes can vary widely between

countries.^{9,12–14} This variation may be due to differences in evidence interpretation that might raise questions regarding the accountability for reasonableness of health systems (deliberation about fair decisions under resource constraints),¹⁵ or due to absence of robust data on the clinical benefit of new cancer medicines available at the time of marketing authorisation,¹⁶ thereby confounding HTA agencies' ability to evaluate key benefit dimensions.

Value frameworks have been developed as decision-support tools in various contexts, including for coverage decisions by health systems and for shared decision making by clinicians and patients,^{17,18} with several focusing on cancer therapies, such as the European Society for Medical Oncology-Magnitude of Clinical Benefit Scale (ESMO-MCBS),^{18,19} among others.^{20–23} The ESMO-MCBS assesses new cancer medicines' magnitude of clinical benefit via a clinician-validated scoring template, which considers the therapies' prognostically weighted benefits (both relative and absolute) with respect to prespecified thresholds, adverse effects, and effect on quality of life.²⁴ Several studies have used the ESMO-MCBS to assess the benefit of cancer medicines from both a regulatory and an HTA perspective.^{14,24–26}

In this study, we used a custom-made, comprehensive dataset to identify which factors were associated with final HTA outcomes and the speed at which positive outcomes were reached; additionally, we examined whether the ESMO-MCBS, as a proxy for clinical benefit, can be used to predict the HTA outcome, having controlled for a number of variables that had not been considered in previous studies following a search to identify relevant literature (appendix p 6).

See Online for appendix

Methods

Study settings and sample selection

In this retrospective analysis, six country settings and their respective HTA agencies were selected: Australia (Pharmaceutical Benefits Advisory Committee [PBAC]); Canada (the pan-Canadian Oncology Drug Review [pCODR], of the Canadian Agency for Drugs and Technologies in Health [renamed to Canada's Drug Agency on May 1, 2024]); England (the National Institute for Health and Care Excellence [NICE]); France (Haute Autorité de Santé [HAS]); the Canadian province of Quebec (Institut National d'Excellence en Santé et en Services Sociaux [INESSS]); and Scotland (Scottish Medicines Consortium [SMC]).

The criteria based on which countries were selected included the study of different HTA models, such as comparative clinical benefit assessment (HAS) versus cost-effectiveness (INESSS, NICE, PBAC, pCODR, and SMC); operational longevity of the HTA agency and stability in the conduct of HTAs; rigorous and transparent methodologies; systematic integration into the health system; and public availability of HTA reports (appendix p 7).

To ensure consistency and comparability, the study sample was limited to new cancer medicines for treating solid tumours in a non-curative setting with published ESMO-MCBS scores and that had been assessed by at least three HTA agencies between Jan 1, 2011, and Dec 31, 2020. Additionally, medicines assessed by HTA agencies based on indirect comparisons or using academic in-confidence data as the main evidence supporting the clinical benefit assessment, rather than including clinical trial results, were not included.

Data collection

We used a methodological framework (appendix pp 14–15) to systematically capture the key elements considered by HTA agencies when making coverage and reimbursement recommendations. Selection of these elements was based on evidence from the literature on decision criteria, both clinical and economic, but also disease-specific and contextual considerations that apply in different settings.¹⁰ Data were extracted from publicly available HTA reports, published clinical trial results, and other sources (ie, reports from regulatory authorities and the medicines' summary of product characteristics). The unit of measurement in the data extraction process was the medicine–indication pair (ie, a medicine for a specific indication), recognising that some medicines might be used for several indications.

The data were extracted by authors EV and PK, and any discrepancies that arose were resolved by consensus between the two authors. The variables used (appendix pp 16–18 for definitions and pp 47–51 for methodological clarifications) were coded and recorded in Microsoft Excel (version 16.89).

Statistical analysis

The ESMO-MCBS uses a scoring system that categorises cancer medicines into different levels of clinical benefit. In the non-curative setting, the focus of this study, the scale ranges from 1 to 5, with scores of 4 or 5 defined as high scores and indicating substantial additional clinical benefit relative to the standard of care, which are good candidates for reimbursement, whereas scores of 1, 2 or 3 are considered low or average additional clinical benefit.^{18,19} Our hypothesis was that substantial clinical benefit defined by an ESMO-MCBS score of 4 or 5 in the non-curative setting is associated with positive HTA outcomes and a shorter time interval between marketing authorisation and a positive HTA outcome than for ESMO-MCBS scores below 4. Furthermore, we hypothesised that product-specific and country-specific characteristics, including evidence uncertainties, and social value judgments, also influence HTA processes and final outcomes. Data were analysed descriptively, followed by multivariable regression analyses. The descriptive analysis reports on the presence of an association between specific variables and HTA outcomes. These variables included ESMO-MCBS score, orphan

designation, the type of risk sharing agreement (if it existed), the marketing authorisation pathway, the time from marketing authorisation to HTA outcome, resubmission status, clinical restrictions, key parameters from the pivotal clinical trial that were submitted for consideration, consideration of clinical and economic uncertainties by HTA agencies, and social value judgements that might influence decision making. Frequencies (χ^2 tests) or continuous data (one-way ANOVA) were compared against the HTA outcome (defined as unrestricted, denoted as “List”; restricted, denoted as “List With Constraints”; and rejected, denoted as “Do Not List”; expanded definitions of HTA outcomes are provided in the appendix p 46).

An analytical framework capturing potential factors associated with market entry and reimbursement of new cancer medicines by health systems (appendix pp 42–44) was used to inform statistical analysis, which was implemented in two separate analyses. First, a Cox proportional hazards model was used to assess the effect of several explanatory variables on the time from marketing authorisation to positive HTA outcome (unrestricted or restricted), including the type of marketing authorisation process, the cancer medicines’ funding modalities, the ESMO-MCBS score, and various product-specific variables as regressors and included country-relevant (fixed) effects including those relating to the country’s HTA system, and time in terms of the year of assessment for each medicine–indication pair (appendix pp 52–53). The method of maximum partial likelihood was used to estimate the parameters in the Cox models and generated the hazard ratio along with standard error, p value, and 95% CIs. Second, a multinomial logistic regression model was used to study the factors associated with the final HTA outcome, including ESMO-MCBS score (to indicate the magnitude of the clinical benefit variable), several clinical variables, evidence uncertainty raised by HTA agencies, social value judgments, type of marketing authorisation process, various product-specific variables, country-specific (fixed) effects including those relating to the country’s HTA system, and time fixed effects as regressors (appendix pp 53–55). Country and time-relevant (fixed) effects controlled for variables that can vary between settings and over time, respectively. The multinomial logistic regression used maximum likelihood estimation to calculate relative risk ratios (RRR), p values, and 95% CIs for the exposed groups relative to the control group. The RRR of a coefficient indicated how the risk of the outcome falling in the comparison group (“List” or “List with Constraints”) compared with the risk of the outcome falling in the referent group (“Do Not List”) changes with the variable in question. We also calculated marginal effects, to describe the average effect of changes in the explanatory variable (ESMO-MCBS score) on the change in the probability of HTA outcomes and time to HTA outcome. Marginal effects were calculated by taking the derivative of the outcome variable with respect to the predictor of interest. In statistical analyses,

the unit of analysis was the medicine–indication–country triplet, which we refer to as HTA submissions.

Analyses were done with Stata (version 16). Standard errors were clustered at the country level. Effect estimates

	HTA outcome			Total (n=360)
	List (n=18)	List with Constraints (n=295)	Do Not List (n=47)	
Regulatory and product characteristics				
HTA agency ($\chi^2=37.59$, Fisher’s exact p=0.0002)				
pCODR (Canada)	1 (6%)	51 (17%)	8 (17%)	60 (17%)
HAS (France)	11 (61%)	51 (17%)	5 (11%)	67 (19%)
INESSS (Quebec)	0	44 (15%)	14 (30%)	58 (16%)
NICE (England)	2 (11%)	57 (19%)	6 (13%)	65 (18%)
PBAC (Australia)	0	40 (14%)	10 (21%)	50 (14%)
SMC (Scotland)	4 (22%)	52 (18%)	4 (9%)	60 (17%)
ESMO-MCBS score ($\chi^2=28.57$, Fisher’s exact p<0.0001)				
1	1 (6%)	23 (8%)	10 (21%)	34 (9%)
2	3 (17%)	36 (12%)	11 (23%)	50 (14%)
3	3 (17%)	88 (30%)	18 (38%)	109 (30%)
4	10 (56%)	131 (44%)	4 (9%)	145 (40%)
5	1 (6%)	17 (6%)	4 (9%)	22 (6%)
ESMO-MCBS score, binary variable ($\chi^2=19.56$, Fisher’s exact p=0.0017)				
Low or average (score 1–3)	7 (39%)	147 (50%)	39 (83%)	193 (54%)
High (score 4 or 5)	11 (61%)	148 (50%)	8 (17%)	167 (46%)
Orphan designation* ($\chi^2=1.17$, Fisher’s exact p=0.51)				
No	15 (83%)	268 (91%)	43 (91%)	326 (91%)
Yes	3 (17%)	27 (9%)	4 (9%)	34 (9%)
Risk-sharing agreement and special funding ($\chi^2=149.70$, Fisher’s exact p<0.0001)				
None	17 (94%)	57 (19%)	47 (100%)	121 (34%)
Risk-sharing agreement	1 (6%)	200 (68%)	0	201 (56%)
Special funding (non-risk sharing agreement)	0	38 (13%)	0	38 (11%)
Resubmission after previous rejection ($\chi^2=4.39$, Fisher’s exact p=0.11)				
No	17 (94%)	223 (76%)	39 (83%)	279 (78%)
Yes	1 (6%)	72 (24%)	8 (17%)	81 (23%)
Marketing authorisation pathway ($\chi^2=5.21$, Fisher’s exact p=0.22)				
Standard	15 (83%)	181 (61%)	27 (57%)	223 (62%)
Accelerated	3 (17%)	61 (21%)	10 (21%)	74 (21%)
Parallel review	0	53 (18%)	10 (21%)	63 (18%)
Clinical restrictions ($\chi^2=47.03$, Fisher’s exact p<0.0001)				
No clinical restrictions	18 (100%)	161 (55%)	47 (100%)	226 (63%)
Population restriction	0	98 (33%)	0	98 (27%)
Prescribing restriction	0	19 (6%)	0	19 (5%)
Population and prescribing restrictions	0	17 (6%)	0	17 (5%)
Months from marketing authorisation to HTA outcome (Prob > F=0.1679)†				
Mean (log-normal SD)	7.4 (0.47)	11.8 (0.89)	11.8 (0.83)	11.6 (12.5)
Minimum	3.0	0.0	0.0	0.0
Maximum	19.0	70.0	81.0	81.0
HTA model ($\chi^2=23.78$, Fisher’s exact p<0.0001)				
Clinical benefit assessment model	11 (61%)	51 (17%)	5 (11%)	67 (19%)
Clinical and cost-effectiveness model	7 (39%)	244 (83%)	42 (89%)	293 (81%)

(Table 1 continues on next page)

	HTA outcome			Total (n=360)
	List (n=18)	List with Constraints (n=295)	Do Not List (n=47)	
(Continued from previous page)				
Characteristics of pivotal trial‡				
Type of trial ($\chi^2=4.63$, Fisher's exact p=0.12)				
Phase 3 trial	17 (94%)	262 (89%)	37 (78%)	316 (88%)
Other phase trial	1 (6%)	33 (11%)	10 (21%)	44 (12%)
Type of trial primary endpoint assessed by ESMO ($\chi^2=5.45$, Fisher's exact p=0.070)				
Surrogate endpoint: progression-free survival or overall response rate				
Surrogate endpoint: progression-free survival or overall response rate	6 (33%)	180 (61%)	27 (57%)	213 (59%)
Clinical endpoint: overall survival§	12 (67%)	115 (39%)	20 (43%)	147 (41%)
Type of trial endpoints considered by HTA agencies ($\chi^2=5.42$, Fisher's exact p=0.49)				
Overall survival				
Overall survival	10 (56%)	77 (26%)	15 (32%)	102 (28%)
Overall survival and progression-free survival (co-primary)				
Overall survival and progression-free survival (co-primary)	2 (11%)	38 (13%)	5 (11%)	45 (13%)
Progression-free survival				
Progression-free survival	6 (33%)	139 (47%)	20 (43%)	165 (46%)
Overall response rate				
Overall response rate	0	41 (14%)	7 (15%)	48 (13%)
Type of trial comparator in the pivotal trial ($\chi^2=8.58$, Fisher's exact p=0.013)				
No active comparator				
No active comparator	5 (28%)	132 (45%)	30 (64%)	167 (46%)
Active comparator				
Active comparator	13 (72%)	163 (55%)	17 (36%)	193 (54%)
Type of trial blinding ($\chi^2=2.49$, Fisher's exact p=0.27)				
Double blind				
Double blind	9 (50%)	128 (43%)	26 (55%)	163 (55%)
Open label				
Open label	9 (50%)	167 (57%)	21 (45%)	197 (45%)
Social value judgements				
Administration advantage ($\chi^2=3.69$, Fisher's exact p=0.17)				
Considered				
Considered	3 (17%)	116 (39%)	18 (38%)	137 (38%)
Not considered				
Not considered	15 (83%)	179 (61%)	29 (62%)	223 (62%)
Unmet medical need¶ ($\chi^2=1.51$, Fisher's exact p=0.48)				
Considered				
Considered	15 (83%)	213 (72%)	32 (68%)	260 (72%)
Not considered				
Not considered	3 (17%)	82 (28%)	15 (32%)	100 (28%)
Disease severity ($\chi^2=1.92$, Fisher's exact p=0.41)				
Considered				
Considered	12 (67%)	148 (50%)	23 (49%)	183 (51%)
Not considered				
Not considered	6 (33%)	147 (50%)	24 (51%)	177 (49%)
Innovation ($\chi^2=1.93$, Fisher's exact p=0.41)				
Considered				
Considered	6 (33%)	99 (34%)	11 (23%)	116 (32%)
Not considered				
Not considered	12 (67%)	196 (66%)	36 (77%)	244 (68%)
Clinical and economic uncertainties raised by HTA agencies				
Uncertainties around the magnitude of clinical benefit ($\chi^2=10.79$, Fisher's exact p=0.0057)				
Recorded				
Recorded	5 (28%)	178 (60%)	34 (72%)	217 (60%)
Not recorded				
Not recorded	13 (72%)	117 (40%)	13 (28%)	143 (40%)
Uncertainties around adverse events that emerged in the pivotal trial ($\chi^2=6.22$, Fisher's exact p=0.046)				
Recorded				
Recorded	4 (22%)	95 (32%)	23 (49%)	122 (34%)
Not recorded				
Not recorded	14 (78%)	200 (68%)	24 (51%)	238 (66%)
Uncertainties around generalisability of the pivotal trial to the population and to clinical practice ($\chi^2=0.94$, Fisher's exact p=0.70)				
Recorded				
Recorded	4 (22%)	98 (33%)	15 (32%)	117 (32%)
Not recorded				
Not recorded	14 (78%)	197 (67%)	32 (68%)	243 (68%)
Uncertainties around the economic modelling submitted by the manufacturer to HTA agencies ($\chi^2=4.98$, Fisher's exact p=0.087)				
Recorded				
Recorded	5 (28%)	161 (55%)	26 (55%)	192 (53%)
Not recorded				
Not recorded	13 (72%)	134 (45%)	21 (45%)	168 (47%)

(Table 1 continues on next page)

are presented with 95% CIs and differences were reported as statistically significant at a p value of less than 0.05.

Role of the funding source

There was no funding source for this study.

Results

In total, 67 medicine–indication pairs met the selection criteria, resulting in 360 HTA submissions (medicine–indication–country triplets; appendix pp 8–13), accounting for 67 (56%) of 119 solid tumour cancer medicine–indication pairs approved by the respective regulatory authorities in the study countries over the 2011–20 study period.

Table 1 presents descriptive statistics for the HTA submissions. 313 (87%) of 360 submissions had a positive HTA outcome (unrestricted, List; or restricted, List with Constraints). Of the 313 HTA submissions that had a positive HTA outcome, 159 (51%) had a high ESMO-MCBS score (4 or 5; table 1). Among 18 HTA submissions that had an unrestricted (List) recommendation, 11 (61%) had an ESMO-MCBS score of 4 or 5 (figure 1).

193 (54%) of 360 HTA submissions had a low or average ESMO-MCBS score (1, 2, or 3). These submissions were disproportionately represented among those with a negative HTA outcome (Do Not List), with 39 (83%) of 47 rejected applications having an ESMO-MCBS score of 3 or lower (table 1, figure 1).

In 36 (54%) of 67 medicine–indication pairs, HTA outcomes were in concordance, with a List or List with Constraints outcome across HTA agencies that provided a recommendation, but 25 (37%) medicine–indication pairs showed discordance (ie, List with Constraints vs Do Not List) and six (9%) medicine–indication pairs showed strong discordance (ie, List vs Do Not List; appendix pp 19–34). Additionally, the relationship between ESMO-MCBS score and HTA outcome was not always congruent (figure 1, table 1), and in some cases, the HTA outcome was in discordance with ESMO-MCBS score. For example, in eight cases, the medicine–indication pair had a high ESMO-MCBS score but was rejected by the HTA agency (appendix p 35).

The relationship between the evidentiary basis for submission to an HTA agency (ie, the primary endpoint used in the pivotal clinical trial) and HTA outcome is presented in table 1 and figure 2. We found that a surrogate endpoint (progression-free survival and objective response rate) was the most frequently considered primary endpoint across the HTA agencies, accounting for 213 (59%) of 360 HTA outcomes, followed by a clinical endpoint (ie, overall survival), which accounted for 147 (41%) HTA outcomes. Surrogate endpoints were the most frequently considered endpoints for List with Constraints and Do Not List outcomes, whereas for a List outcome, clinical endpoints were considered in 12 (67%) of 18 cases (including two cases in

which a clinical endpoint [overall survival] was a co-primary endpoint with a surrogate endpoint [progression-free-survival] and surrogate endpoints were considered in six (33%) cases.

81 (23%) of 360 HTA submissions were for a medicine-indication for which there was at least one previous HTA rejection (Do Not List) by the same HTA agency, having previously failed to satisfy HTA agencies on one or more criteria, such as the quality of evidence, the magnitude of clinical benefit, or clinical or economic uncertainties. Of these 81 resubmissions, 73 (90%) were subsequently approved by the HTA agency, while the remaining eight (10%) had a negative HTA outcome (table 1).

Numerous clinical and economic restrictions were identified, resulting in a List with Constraints designation. 134 (43%) of 313 positive HTA outcomes were subject to one or more clinical restrictions; 98 (31%) of 313 were population related, 19 (6%) were prescribing related, and 17 (5%) were related to both (table 1). Economic restrictions, designed to improve affordability, were common; 201 (64%) of 313 positive HTA outcomes (200 with a List with Constraints outcome and one with a List outcome) had a risk-sharing agreement attached to them, while 38 (12%) received a List with Constraints outcome via a special funding scheme (non-risk-sharing agreement; table 1), such as inclusion in the Cancer Drugs Fund in England, or in the New Drug Funding Programme or Exceptional Access Programme in Canada.

Notable variations were found with respect to the time to HTA outcome after marketing authorisation. When stratified marketing authorisation pathway, pCODR (Canada) had the shortest interval, with a mean time to HTA outcome of 8.4 (log-normal SD 0.89) months between marketing authorisation and HTA outcome, whereas NICE (England) had the longest, with a mean time of 17.1 (0.83) months (appendix p 48). Across the HTA agencies considered, negative (Do Not List) and restricted positive (List with Constraints) HTA outcomes took longer than an unrestricted (List) outcome, with mean times of 11.8 (log-normal SD 0.83) months, 11.8 (0.89) months, and 7.4 (0.47) months, respectively (table 1).

Among the 360 HTA submissions, 74 (21%) received marketing authorisation under an accelerated approval process and 63 (18%) underwent parallel review in which the licensing and HTA evaluations were done simultaneously. The remaining 223 (62%) underwent a standard marketing authorisation process (table 1). Our analysis showed that therapies approved via an accelerated process had a longer time to HTA outcome than therapies approved via the standard process, with a mean time of 15.2 (log-normal SD 0.79) months versus 12.2 (0.84) months, respectively, between marketing authorisation and a HTA outcome. By contrast, therapies that underwent parallel review had a comparatively short interval between marketing authorisation and HTA outcome; for each of the three HTA agencies that performed parallel reviews, the mean times were 4.2

	HTA outcome			Total (n=360)
	List (n=18)	List with Constraints (n=295)	Do Not List (n=47)	
(Continued from previous page)				
Uncertainties around the clinical and cost inputs to the economic model ($\chi^2=11.94$, Fisher's exact p=0.0018)				
Recorded	2 (11%)	119 (40%)	27 (57%)	148 (41%)
Not recorded	16 (89%)	176 (60%)	20 (43%)	212 (59%)

Data are n (%) unless otherwise stated. Frequencies (χ^2 tests) or continuous data (one-way ANOVA) were compared by HTA outcome. HTA=health technology assessment. n=HTA submissions (medicine-indication-country triplets). ESMO-MCBS=European Society for Medical Oncology-Magnitude of Clinical Benefit Scale. pCODR=pan-Canadian Oncology Drug Review. HAS=Haute Autorité de Santé. INESSS=Institut National d'Excellence en Santé et Services Sociaux. NICE=National Institute for Health and Care Excellence. PBAC=Pharmaceutical Benefits Advisory Committee. SMC=Scottish Medicines Consortium. *According to European Medicines Agency designation. †The ANOVA test indicated that there were no significant differences as p>0.05. ‡The pivotal clinical trial was the study seeking to show the efficacy of a new therapy in order to obtain marketing authorisation by a regulatory authority. §Including the cases (n=2) when overall survival was combined with progression-free survival as a co-primary endpoint. ¶As defined by each HTA agency.

Table 1: Descriptive statistics for HTA submissions of cancer medicines for solid tumours in a non-curative setting

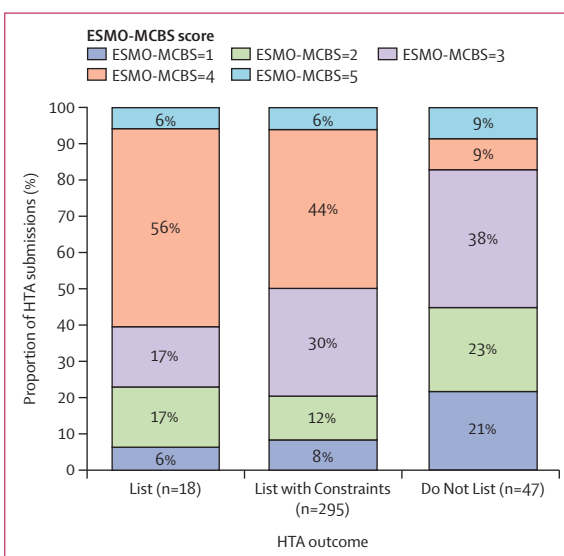


Figure 1: Relationship between ESMO-MCBS score and HTA outcomes
n=HTA submissions (medicine-indication-country triplets).

ESMO-MCBS=European Society for Medical Oncology-Magnitude of Clinical Benefit Scale. HTA=health technology assessment.

(log-normal SD 0.64) months for pCODR (Canada), 5.6 (1.23) months for PBAC (Australia), and 7.0 (0.53) months for INESSS (Quebec), respectively (figure 3), with an overall mean of 5.5 (0.78) months.

Table 2 summarises the results of our Cox proportional hazards model (additional results and details in the appendix [pp 36–38, 56]). Our analysis showed that accelerated marketing authorisation was significantly associated with a longer time to positive HTA outcome (List or List with Constraints) than therapies that were approved via the standard process (hazard ratio [HR] per 1 month increment 0.70 [95% CI 0.51–0.95], p=0.024).

For the European Medicines Agency orphan designation see <https://www.ema.europa.eu/en/human-regulatory/overview/orphan-designation-overview>

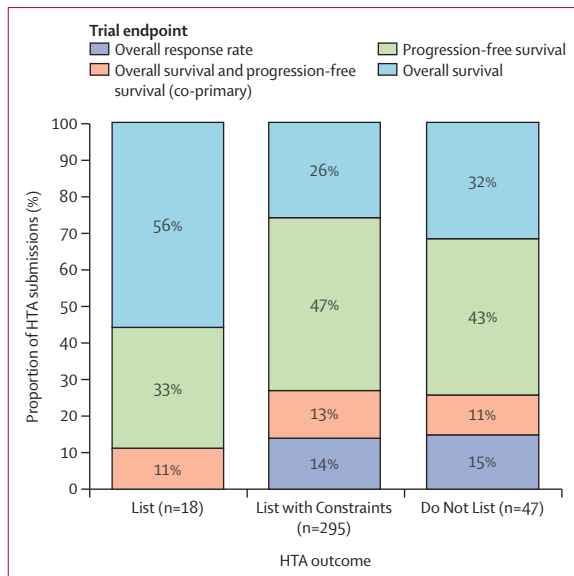


Figure 2: Relationship between trial endpoints considered by HTA agencies and the HTA outcome
n=HTA submissions (medicine-indication-country triplets).

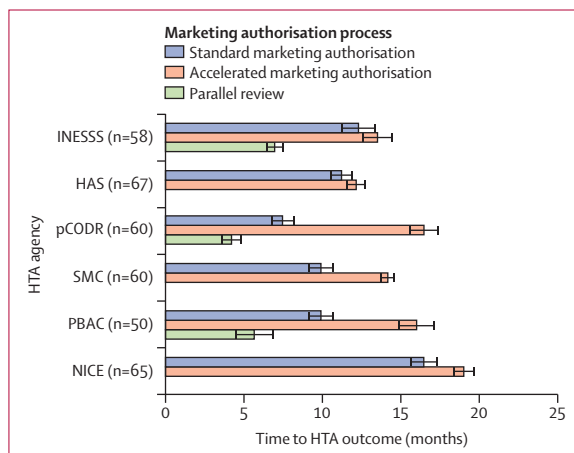


Figure 3: Time from marketing authorisation to HTA outcome by type of marketing authorisation process and HTA agency
Bars represent the mean; error bars are SDs based on log-normal distribution. HTA=health technology assessment. INESSS=Institut National d'Excellence en Santé et Services Sociaux (Canadian province of Quebec). HAS=Haute Autorité de Santé (France). pCODR=pan-Canadian Oncology Drug Review (Canada). SMC=Scottish Medicines Consortium (Scotland). PBAC=Pharmaceutical Benefits Advisory Committee (Australia). NICE=National Institute for Health and Care Excellence (England). n=HTA submissions (medicine-indication-country triplets).

A parallel review process was significantly associated with a shorter time to positive HTA outcome than the standard review process (HR 1.69 [1.13–2.54], $p=0.011$). A high ESMO-MCBS score was significantly associated with a shorter time to positive HTA outcome than a low or average ESMO-MCBS score (HR 1.42 [1.11–1.81], $p=0.0055$). Having calculated the marginal predictions for time to positive HTA outcomes based on either a low or average ESMO-MCBS score or a high ESMO-MCBS

score, accounting for all confounders in our model, we found that a high ESMO-MCBS score significantly decreased the time to positive HTA outcome from 13.1 (95% CI 11.5–14.7) months to 9.8 (8.0–11.5) months ($p<0.0001$; appendix pp 4, 57). Having a risk-sharing agreement was significantly associated with a shorter time to positive HTA outcome (HR 4.62 [95% CI 2.51–8.51], $p<0.0001$). Similarly, the presence of special funding arrangements was significantly associated with a shorter time to positive HTA outcome (HR 4.16 [2.03–8.50], $p=0.0001$). Assessment in Canada (HR 2.82 [1.68–4.75], $p=0.0001$) and France (HR 5.70 [2.87–11.33], $p<0.0001$) was significantly associated with a shorter time to positive HTA outcome versus appraisal in England, whereas assessment in Quebec, Australia, and Scotland were not. Orphan designation and year of HTA outcome were not found to be significantly associated with a positive HTA outcome.

In multinomial regression, factors that were associated with a positive HTA outcome (List or List with Constraints) included the type of marketing authorisation process, product characteristics, clinical characteristics, evidence uncertainties, social value judgments, and country-relevant effects (table 3, appendix pp 39–40). A high ESMO-MCBS score (*vs* a low or average score) was significantly associated with a positive HTA outcome (both unrestricted [List], relative risk ratio [RRR] 14.10 [95% CI 3.54–56.20], $p=0.0002$; and restricted [List with Constraints], RRR 4.52 [1.90–10.75], $p=0.0006$). In terms of the predicted probability of receiving a positive HTA outcome (either List or List with Constraints), accounting for all confounders in our model, we found that a high ESMO-MCBS score was associated with a 96.5% probability (95% CI 93.8–99.2) of achieving a positive HTA listing; having a low or average ESMO-MCBS score was associated with an 84.6% probability (78.5–90.6) of achieving a positive HTA outcome, representing a significant difference ($p<0.0001$; appendix pp 4, 57). This difference appeared to be driven primarily by therapies that had an ESMO-MCBS score of 3, followed by therapies with an ESMO-MCBS score of 1 or 2 (figure 1).

In addition to the statistical significance of high ESMO-MCBS score in predicting unrestricted (List) and restricted (List with Constraints) positive HTA outcomes, other model parameters were significant predictors (table 3). Resubmission was positively associated with a List without Constraints outcome (*vs* no resubmission, RRR 2.56 [1.45–4.50], $p=0.0011$), and orphan designation was positively associated with a List outcome (RRR 6.78 [2.30–19.99], $p=0.0005$). Having a clinical endpoint (*vs* no clinical endpoint) in the pivotal trial was significantly less likely to be associated with a List with Constraints outcome (RRR 0.31 [0.17–0.59], $p=0.0003$), and an active trial comparator (*vs* no active comparator) was significantly more likely to be associated with a List outcome (RRR 4.00 [1.32–12.10], $p=0.014$). Uncertainties raised by

HTA agencies regarding the robustness of the clinical and economic evidence were associated with HTA outcomes. Uncertainties regarding the magnitude of clinical benefit were negatively associated with an unrestricted HTA outcome (uncertainties recorded *vs* not recorded, RRR 0.06 [0.01–0.36], $p=0.0020$). Uncertainties about economic evidence (ie, inputs to the economic model, such as possible cost underestimates or concerns regarding the utilities used in quality-adjusted life year calculations) were significantly less likely to have been raised in cases in which there was an unrestricted or restricted positive HTA outcome (uncertainties recorded *vs* not recorded, RRR 0.28 [0.10–0.78], $p=0.014$ and RRR 0.45 [0.25–0.82], $p=0.010$, respectively). Acknowledgment by HTA agencies that the medicine addressed an unmet medical need was significantly associated with positive unrestricted and restricted HTA outcomes (*vs* unmet need not recorded, RRR 22.73 [5.51–93.73], $p<0.0001$, and RRR 1.87 [1.18–2.97], $p=0.0075$, respectively). Benefits derived from a reduced burden of administration were significantly less likely to be recorded in unrestricted recommendations (administration advantage recorded *vs* not recorded, RRR 0.07 [0.02–0.21], $p<0.0001$). All other factors assessed were not found to be associated with HTA outcomes.

Country-relevant effects revealed significant differences between countries for unrestricted (List) and restricted (List with Constraints) HTA outcomes; HTA agencies in France and Scotland were significantly more likely to recommend cancer medicines without restrictions than in England (RRR 49.65 [12.35–199.60], $p<0.0001$, and RRR 18.23 [7.53–44.16], $p<0.0001$, respectively). By contrast, HTA agencies in Quebec and Australia were significantly less likely to recommend cancer medicines with restrictions (RRR 1.15×10^{-6} [1.44×10^{-7} – 9.09×10^{-6}], $p<0.0001$, and RRR 1.78×10^{-6} [1.04×10^{-8} – 3.00×10^{-4}], $p<0.0001$, respectively) and without restrictions (RRR 0.33 [0.24–0.46], $p<0.0001$, and RRR 0.30 [0.15–0.61], $p=0.0008$, respectively) than in England. A List with Constraints recommendation was also significantly less likely to be made in Canada than in England (RRR 0.64 [0.45–0.91], $p=0.012$; table 3). No other country-relevant effects were found.

Discussion

In this study, we outlined and empirically tested a model that comprehensively mapped factors associated with HTA agency recommendations for the coverage and reimbursement of new cancer medicines. We also found evidence that these recommendations are influenced by the potential of medicines to provide substantial clinical benefit, such that high ESMO-MCBS scores were associated with both a reduced interval between marketing authorisation and positive (restricted or unrestricted) HTA outcomes and an increased likelihood of achieving a positive (restricted or unrestricted) HTA outcome compared with low or average ESMO-MCBS scores.

	HR (95% CI)	p value
Marketing authorisation process		
Accelerated (<i>vs</i> standard)	0.70 (0.51–0.95)	0.024
Parallel review (<i>vs</i> standard)	1.69 (1.13–2.54)	0.011
Product characteristics		
Orphan designation (<i>vs</i> non-orphan)	1.33 (0.88–1.99)	0.17
Funding mechanism		
Risk-sharing agreement (<i>vs</i> no funding agreement)	4.62 (2.51–8.51)	<0.0001
Special funding (<i>vs</i> no funding agreement)	4.16 (2.03–8.50)	0.0001
Clinical evidence		
High ESMO-MCBS score (<i>vs</i> low or average ESMO-MCBS score) [†]	1.42 (1.11–1.81)	0.0055
Time effect [‡]		
Year of HTA recommendation (per 1 calendar year increment)	0.96 (0.91–1.01)	0.11
Country-relevant (fixed) effects [‡]		
Canada, pCODR (<i>vs</i> England, NICE)	2.82 (1.68–4.75)	0.0001
France, HAS (<i>vs</i> England, NICE)	5.70 (2.87–11.33)	<0.0001
Quebec, INESSS (<i>vs</i> England, NICE)	1.30 (0.84–2.01)	0.23
Australia, PBAC (<i>vs</i> England, NICE)	1.39 (0.83–2.33)	0.22
Scotland, SMC (<i>vs</i> England, NICE)	1.43 (0.99–2.08)	0.057
Observations per variable	344§	..

Variables in parentheses are the reference. HRs represent a 1 month increment (dependent variable) unless otherwise indicated. Standard errors clustered at the country level are provided in the appendix (p 36). HTA=health technology assessment. HR=hazard ratio. ESMO-MCBS=European Society for Medical Oncology-Magnitude of Clinical Benefit Scale. pCODR=pan-Canadian Oncology Drug Review. NICE=National Institute for Health and Care Excellence. HAS=Haute Autorité de Santé. INESSS=Institut National d'Excellence en Santé et Services Sociaux. PBAC=Pharmaceutical Benefits Advisory Committee. SMC=Scottish Medicines Consortium. *The test of proportional hazards assumption of the Cox regression showed that the variable of "resubmission" did not satisfy the proportional hazards assumption ($p=0.0044$); therefore, the model was stratified for this variable (appendix p 36). †High ESMO-MCBS score=4 or 5; low or average ESMO-MCBS score=1, 2, or 3. ‡Control variables. §The Cox model censored observations with zero time to the event; thus cases where drugs were already approved for reimbursement before receiving marketing authorisation ($n=16$ by PBAC) were excluded.

Table 2: Analysis of factors associated with time to a positive HTA outcome (List or List with Constraints) in stratified Cox proportional hazards regression*

Additionally, several product-specific characteristics, such as orphan designation, and contextual factors, such as unmet medical need and ease of administration, were associated with positive HTA outcomes. Uncertainty regarding the magnitude of clinical benefit was more likely to adversely affect an unrestricted HTA recommendation than uncertainty regarding economic evidence; and country-relevant effects showed considerable differences among countries, affecting restricted and unrestricted HTA outcomes.

Our study makes four distinct contributions to the literature: first, it proposes a new value framework of factors associated with positive HTA outcomes, which shape reimbursement decisions for cancer medicines. Second, to our knowledge, this is the first study to quantitatively evaluate whether the ESMO-MCBS and other parameters, including social value judgements and evidence uncertainties, predict positive HTA outcomes. Third, to our knowledge, it is the first study to quantitatively evaluate whether a high ESMO-MCBS score and other parameters lead to faster positive HTA decisions.

	Association with List outcome (vs Do Not List)		Association with List with Constraints outcome (vs Do Not List)	
	RRR (95% CI)	p value	RRR (95% CI)	p value
Marketing authorisation process				
Accelerated (vs standard)	1.69 (0.71–4.04)	0.24	0.81 (0.38–1.75)	0.59
Parallel review (vs standard)	8.79×10 ⁻⁶ (6.18×10 ⁻⁷ –1.00×10 ⁻⁴)	<0.0001	1.39 (0.60–3.23)	0.45
Product characteristics				
Resubmission (vs no resubmission)	0.33 (0.02–6.45)	0.47	2.56 (1.45–4.50)	0.0011
Orphan designation (vs non-orphan)	6.78 (2.30–19.99)	0.0005	1.14 (0.31–4.18)	0.84
Clinical evidence				
High ESMO-MCBS score (vs low or average ESMO-MCBS score)*	14.10 (3.54–56.20)	0.0002	4.52 (1.90–10.75)	0.0006
Clinical endpoint (vs no clinical endpoint)	1.06 (0.74–1.53)	0.75	0.31 (0.17–0.59)	0.0003
Active trial comparator (vs no active trial comparator)	4.00 (1.32–12.10)	0.014	1.12 (0.58–2.16)	0.73
Double-blind trial (vs open label)	3.56 (0.84–15.03)	0.085	0.79 (0.27–2.31)	0.67
Uncertainties				
Recorded uncertainties relating to the magnitude of clinical benefit (vs not recorded)	0.06 (0.01–0.36)	0.0020	0.70 (0.39–1.27)	0.24
Recorded uncertainties in generalisability (vs not recorded)	0.81 (0.06–10.27)	0.87	1.34 (0.69–2.58)	0.38
Recorded uncertainties in the economic modelling (vs not recorded)	2.26 (0.34–14.92)	0.40	1.69 (0.57–4.96)	0.34
Recorded uncertainties in inputs to economic model (vs not recorded)	0.28 (0.10–0.78)	0.014	0.45 (0.25–0.82)	0.010
Social value judgements				
Disease severity recorded (vs not recorded)	0.45 (0.13–1.54)	0.20	0.57 (0.30–1.06)	0.078
Innovation recorded (vs not recorded)	4.08 (0.53–31.15)	0.18	1.15 (0.29–4.57)	0.84
Administration advantage recorded (vs not recorded)	0.07 (0.02–0.21)	<0.0001	0.71 (0.26–1.90)	0.49
Unmet medical need recorded (vs not recorded)	22.73 (5.51–93.73)	<0.0001	1.87 (1.18–2.97)	0.0075
Country-relevant (fixed) effects†				
Canada, pCODR (vs England, NICE)	0.74 (0.15–3.72)	0.71	0.64 (0.45–0.91)	0.012
France, HAS (vs England, NICE)	49.65 (12.35–199.60)	<0.0001	1.47 (0.73–2.92)	0.28
Quebec, INESSS (vs England, NICE)	1.15×10 ⁻⁶ (1.44×10 ⁻⁷ –9.09×10 ⁻⁶)	<0.0001	0.33 (0.24–0.46)	<0.0001
Australia, PBAC (vs England, NICE)	1.78×10 ⁻⁶ (1.04×10 ⁻⁸ –3.00×10 ⁻⁴)	<0.0001	0.30 (0.15–0.61)	0.0008
Scotland, SMC (vs England, NICE)	18.23 (7.53–44.16)	<0.0001	1.95 (0.99–3.86)	0.055
Time fixed effects†				
Time fixed effects considered	Yes	..	Yes	..
Model constant	4.31×10 ⁻¹⁰ (1.16×10 ⁻¹¹ –1.60×10 ⁻⁸)	<0.0001	5.80 (1.58–21.29)	0.0081
Observations per variable	360	..	360	..

Variables in parentheses are the reference. Standard errors clustered at the country level are provided in the appendix (pp 39–40). HTA=health technology assessment. RRR=relative risk ratio. SE=clustered standard errors. ESMO-MCBS=European Society for Medical Oncology-Magnitude of Clinical Benefit Scale. pCODR=pan-Canadian Oncology Drug Review. NICE=National Institute for Health and Care Excellence. HAS=Haute Autorité de Santé. INESSS=Institut National d'Excellence en Santé et Services Sociaux. PBAC=Pharmaceutical Benefits Advisory Committee. SMC=Scottish Medicines Consortium. *High ESMO-MCBS score=4 or 5; low or average ESMO-MCBS score=1, 2, or 3. †Control variable.

Table 3: Analysis of factors associated with HTA outcomes in multinomial logistic regression

And, fourth, it captures similarities and differences in value judgements of cancer medicines through comparative analysis of HTA outcomes in countries with well established HTA systems.

The insights gained from this study regarding the decision-making processes of national HTA agencies have several policy implications concerning the HTA

review processes and the use of the ESMO-MCBS as a value framework to inform reimbursement decisions. First, cancer medicines with a high ESMO-MCBS score were associated with a positive HTA outcome. The association was robust, given that it was tested against a number of different model permutations (appendix pp 39–40), as well as being statistically significant and

unaffected by other variables, confirming that the ESMO-MCBS score can serve as a measure of a new therapy's clinical benefit²⁷ and highlighting its value as part of the HTA decision-making process.^{28,29}

Second, although high ESMO-MCBS scores were predictive of positive HTA outcomes, there were cases in which a medicine–indication with a high ESMO-MCBS score was rejected by HTA agencies, and cases in which those with a low or average ESMO-MCBS score were recommended by HTA agencies. These observations underscore the multiplicity of criteria used by HTA agencies to inform coverage decisions. Despite a low ESMO-MCBS score, contextual considerations, such as unmet medical need and the absence of therapeutic alternatives in a particular indication, coupled with a risk-sharing agreement in order to improve cost-effectiveness or have a reasonable budget impact, could lead to a positive HTA outcome. Conversely, a negative HTA outcome, despite a high ESMO-MCBS score, could be due to failure to meet clinical and cost-effectiveness criteria, considerable evidence uncertainties (eg, in terms of generalisability), and the absence of a risk-sharing agreement implying that price or budget impact are unacceptably high.

Third, 37% of HTA outcomes were discordant and 9% were strongly discordant. Although this highlights that HTA processes are unique and country-specific, discordant or very discordant cases in a group of high-income countries could be explained by differences in the interpretation of evidence by HTA agencies, including country-relevant priorities and differences in the perception of clinical and economic uncertainties.

Fourth, uncertainty regarding the robustness of the clinical and economic evidence adversely affected HTA outcomes. We found that concerns raised by decision makers regarding the veracity of the magnitude of clinical benefit data or the cost and utility data included in HTA submissions reduced the likelihood of receiving a positive recommendation. Risk-sharing strategies can act as catalysts when significant clinical or economic uncertainties are present, but, at times, the difference in price expectations between suppliers of medicinal products and health system purchasers might be considered too large, resulting in some new medicines being rejected in some settings but accepted with restrictions in others.

Fifth, social value judgements, particularly unmet medical need, did have a role in HTA decision making, and could act as decision modifiers when the size of clinical benefit, proxied by ESMO-MCBS, is low or modest, implying a higher probability of rejection. In these instances, a risk-sharing agreement can mitigate low cost-effectiveness and high budget impact. For example, tivozanib, licensed for first-line use in patients with metastatic renal cell cancer that has progressed after up to one previous treatment with cytokine therapy, which received an ESMO-MCBS score of 1, was recommended

for funding in Scotland based on significant unmet medical need due to a paucity of tolerable options for patients who might be approaching end-of-life care, and improved cost-effectiveness via a patient access scheme designed to reduce procurement costs.³⁰

Sixth, it took longer for HTA agencies to decide whether to recommend a new cancer medicine when approved via an accelerated marketing authorisation process than when approved via the standard process. Accelerated marketing authorisation is most commonly associated with studies using surrogate endpoints,^{10,16} in which ongoing approval is contingent upon the outcomes of subsequent confirmatory studies. Immature or early-phase evidence typically leads to substantial uncertainty regarding the true clinical benefit and its magnitude, and, consequently, delays the final decision until evidentiary gaps are addressed satisfactorily. HTA agencies commonly adopt a conservative stance regarding these uncertainties, which can substantially increase the time needed to reach a final HTA decision. Although seemingly counterintuitive, this effect is linked to a core function of the HTA process to cautiously interpret the evidence and its generalisability as the basis for making reasonable decisions on resource allocation.

Seventh, although our analysis of the time to positive HTA outcome identified several factors associated with a faster positive HTA recommendation, including high ESMO-MCBS score, the existence of a risk-sharing agreement, and a parallel review process, positive outcomes do not always imply immediate access for patients. Further delays might occur owing to statutory or budgetary reasons; for example, providers might be given some time to secure resources for a new therapy to be covered.

Finally, our findings are generalisable to settings implementing different HTA models, predominantly in high-income countries, to inform coverage decisions for cancer medicines. Contextual considerations, clinical and economic efficiency, and affordability criteria shape coverage decisions in addition to the ESMO-MCBS.

The study has several limitations warranting discussion. First, we relied on publicly available information reported by the various HTA agencies. However, although specific data were often redacted (eg, cost-effectiveness data) or excluded (eg, risk-sharing agreement details, price discounts, or commercial in-confidence data), the available information was sufficiently comprehensive, allowing us to include a wide range of parameters in our analysis. Second, our analysis focused on solid tumours and non-curative treatments. Natural extensions of this study include the analysis of haematological tumours, treatments in curative settings, and application in other settings, for example, upper-middle income countries. Third, the time to positive HTA outcome might underestimate the actual time needed for the medicine to be included in a health system's reimbursement list, due to further negotiations on the terms of coverage by procurement agencies and additional statutory requirements,

such as publication of reimbursement agreements in countries' official publications.

Overall, our analysis suggests that HTA processes can be improved by routine use of a standardised tool such as the ESMO-MCBS score in conjunction with other parameters of benefit, thereby contributing to the harmonisation of methods across settings with respect to assessing the value of new cancer medicines.

Contributors

Conceptualisation: PK. Data curation: PK, EV. Formal analysis: PK, EV. Investigation leads: PK, EV. Methodology: PK, EV, AA. Project administration: PK. Software use: PK, EV. Supervision: PK. Accessed and verified the data: PK, EV. Data visualisation: PK, EV. Access to all data in the study: all authors. Writing (original draft): PK, EV, AA. Writing (review and editing): PK, EV, AA. Final responsibility for the decision to submit for publication: all authors.

Declaration of interests

We declare no competing interests.

Data sharing

The data extracted and used for this study can be made available upon request to the corresponding author (PK) between 6 and 12 months after publication of this Article and upon submission and approval of a proposal by the study authors and with corresponding author support; proposals should be submitted to PK (p.g.kanavos@lse.ac.uk) and if approved, data will be shared by email.

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