Added benefit and revenues of oncology drugs approved by the European Medicines Agency between 1995 and 2020: retrospective cohort study

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ABSTRACT

OBJECTIVES

To evaluate the added benefit and revenues of oncology drugs, explore their association, and investigate potential discrepancies between added benefit and revenues across different approval pathways of the European Medicines Agency (EMA).

DESIGN

Retrospective cohort study.

SETTING

Oncology drugs and their indications approved by the EMA between 1995 and 2020.

MAIN OUTCOME MEASURES

Added benefit was evaluated using ratings published by seven organisations: health technology assessment agencies from the United States, France, Germany, and Italy, two medical oncology societies, and a drug bulletin. All retrieved ratings were recategorised using a four point ranking scale to indicate negative or non-quantifiable, minor, substantial, or major added benefit. Revenue data were extracted from publicly available financial reports and compared with published estimates of research and development (R&D) costs. Finally, the association between added benefit and revenue was evaluated. All analyses were performed within the overall study cohort, and within subgroups based on the EMA approval pathway: standard marketing authorisation, conditional marketing authorisation, and authorisation under exceptional circumstances.

RESULTS

131 oncology drugs with 166 indications were evaluated for their added benefit by at least one organisation within the required timeframe, yielding a total of 458 added benefit ratings; 189 (41%) were negative or non-quantifiable. The median time to offset the median R&D costs ($684m, £535m, €602m, adjusted to 2020 values) was three years; 50 of 55 (91%) drugs recovered these costs within eight years. Drugs with higher added benefit ratings generally had greater revenues. Negative or non-quantifiable added benefit ratings were more frequent for conditional marketing authorisations and authorisations under exceptional circumstances than for standard marketing authorisations (relative risk 1.53, 95% confidence interval 1.23 to 1.89). Conditional marketing authorisations generated lower revenues and took longer to offset R&D costs than standard marketing authorisations (four years compared with three years).

CONCLUSIONS

While revenues seem to align with added benefit, most oncology drugs recover R&D costs within a few years despite providing little added benefit. This is particularly true for drugs approved through conditional marketing authorisations, which inherently appear to lack comprehensive evidence. Policy makers should evaluate whether current regulatory and reimbursement incentives effectively promote development of the most effective drugs for patients with the greatest needs.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Global spending for oncology drugs is projected to rise from $167bn (£132bn; €155bn) in 2020 to $269bn in 2025

Simultaneously, the number of oncology drugs approved is increasingly based on less comprehensive evidence, leading to high rates of negative added benefit ratings

Concerns have been raised about the misalignment of incentives in the pharmaceutical market with patient interests

WHAT THIS STUDY ADDS

This study reveals that a large proportion of oncology drugs approved by the European Medicines Agency between 1995 and 2020 offer minimal or no added benefit, particularly those approved through expedited pathways

Even though the analysis shows an alignment between added benefit and revenues, drugs with lower levels of added benefit were still able to recover their estimated R&D expenses within a relatively short period

Through further collaboration on the interface of drug regulation and reimbursement, opportunities can be explored to incentivise the development of highly beneficial drugs that address urgent unmet needs more effectively

Introduction

The share of cancer care expenditures allocated to oncology drugs is consistently rising, primarily driven by increasing volumes of innovative drugs reaching the market and the high prices associated with these treatments.[1-5] Correspondingly, global spending for oncology drugs is estimated to rise from $167bn (£132bn; €155bn) in 2020 to $269bn in 2025.[6] High prices for oncology drugs are often justified by the need to earn back research and development (R&D) expenses, and by the value these drugs aim to deliver to patients.[7 8] Whether prices are truly justified by the required earnings and the value—or added benefit—that these drugs deliver to patients has been subject to extensive debate.[1 2 9-11]

Health technology assessment (HTA) agencies are among the various organisations that conduct and publish added benefit assessments. The primary objective of HTA is to inform decision makers on the implementation of new health technologies to ensure that the finite resources of a healthcare system are used in an efficient and effective manner. In this context,

added benefit assessments are a key tool for evaluating the value of new drugs, informing clinical practice, and guiding reimbursement decisions.[12] These assessments are based on comparing a drug's effects with those of the best available alternative, informed by relevant evidence. Added benefit assessments go beyond benefit-risk assessments performed by regulatory authorities because benefit-risk assessments are not necessarily comparing a drug's effects with those of the best (nationally) available alternative. The differences between these two types of assessments might lead to drugs with a positive benefit-risk balance but negative added benefit, which is often the case if robust comparative evidence is lacking.[13-16]

Increasingly, oncology drugs are approved based on less comprehensive evidence, such as evidence obtained from non-randomised or single arm trials, or based only on surrogate endpoints that do not directly represent a clinical benefit but might predict one.[2 17 18] A study by Naci and colleagues found that 13 (24%) of the 54 pivotal trials that supported the 32 new oncology drugs approved by the European Medicines Agency (EMA) between 2014 and 2016 were non-randomised or single arm trials.[19] Regulatory authorities acknowledge the unmet medical needs that new innovative treatments might address and have adopted expedited approval pathways to enable patient access, resulting in an increase in the approval of drugs that are associated with less comprehensive evidence.[20] This approach leads to substantial uncertainty at the time reimbursement decisions are made, inherently hampering assessments of added benefit. HTA bodies tend to show greater reluctance in recommending drugs for which there is less comprehensive evidence available, and previous research has shown high proportions of negative added benefit ratings of (oncology) drugs approved through expedited approval pathways.[14 15 18 21 22]

With high prices, increased use of expedited approval pathways, and the consequential difficulties for added benefit assessments, concern is growing that incentives within the pharmaceutical market are not in line with the interests of patients, namely fast and sustainable access to drugs that provide clinical benefits.[3 14 23] Previous research has shown that no statistically significant association exists between estimates of added benefit and drug prices, implying that drugs are not necessarily rewarded for the value they deliver.[2 14 17 23-25] Drugs lacking added benefit are not found to be associated with lower prices compared with drugs that provide greater benefit.[1] However, an important limitation of these studies is that their analyses are often based on public list prices, which are arguably an imperfect measure of financial incentives because they only provide information for a single country and they are usually subject to confidential discounts negotiated by hospitals, insurers, governments, or HTA agencies.[14 23] Focusing on drug revenues might be a valid alternative because these are globally relevant and provide a better reflection of the earnings associated with a drug.

The objectives of this study were to investigate the added benefit of oncology drugs approved by the EMA between 1995 and 2020; assess corresponding cumulative revenues compared with estimated R&D costs; and explore the association between added benefit and revenues. Additionally, we aimed to examine whether discrepancies in added benefit or revenues exist across the various EMA approval pathways; that is, standard marketing authorisation (SMA), conditional marketing authorisation (CMA), and authorisation under exceptional circumstances (AEC). Box 1 presents definitions of key terms.

Methods

To quantify added benefit, we extracted ratings from evaluation reports by several organisations, including HTA agencies from Europe and the United States, medical oncology societies, and a drug bulletin. We analysed the development of global revenues based on publicly available financial reports from pharmaceutical companies and compared them with previously published estimates of R&D expenses. Finally, we integrated these analyses by linking added benefit ratings to corresponding revenue data.

Study cohort and setting

All drugs and their initial indications approved in the European Union since the inception of the EMA in 1995 up to 2020 were retrieved from the EMA's register of European public assessment reports.[28] Veterinary drugs, non-oncology drugs, generics, biosimilars, refused drugs, diagnostics, and duplicates were excluded from the cohort. Non-oncology drugs were identified based on the Anatomical Therapeutical Chemical (ATC) classification system of the World Health Organization.[29]

Ratings of added benefit were obtained from evaluation reports published by organisations including HTA agencies, medical oncology societies, and drug bulletins, with the final selection based on four criteria: the organisations should publish an appraisal or judgment of added benefit; the organisations had to use a multiple category scale to quantify the level of added benefit (eg, absent, minor, moderate, major); the organisations should not incorporate any cost related aspects in their added benefit appraisals (ie, the added benefit rating should not be confounded by costs); and their reports had to be in English, Dutch, French, German, or Italian. Ultimately, this led to the consideration of evaluation reports from the following organisations:

- Institute for Clinical and Economic Review (ICER, a non-profit organisation in the US). The US lacks a centralised HTA agency. While ICER is not formally designated as an HTA agency, it operates as an HTA-like organisation, conducting assessments similar to traditional HTA processes[30]
- Haute Autorité de Santé (HAS, HTA agency of France)
- Gemeinsamer Bundesausschuss (G-BA, HTA agency of Germany). Germany has two HTA organisations: G-BA and the Institut für Qualität

Box 1: Definitions of key terms used throughout this study

Added benefit

The added benefit of a health technology can be defined as its therapeutic value compared with one or more alternative treatments, typically the standard of care within the assessed indication. Added benefit ratings serve different purposes, primarily enabling treatment prioritisation and informing drug related decision making.

Drug-indication combination

Oncology drugs can be approved for and used in several indications. The extent of added benefit for a drug can differ considerably across indications owing to, for example, variations in standards of care. Consequently, evaluations of added benefit apply to specific drug-indication combinations.

Standard marketing authorisation (SMA)

SMA is a type of marketing authorisation that is granted by the European Medicines Agency (EMA) when comprehensive data are available that indicate a positive benefit-risk balance.

Conditional marketing authorisation (CMA)

CMA is a type of marketing authorisation that can be granted by the EMA before comprehensive clinical data are available. CMA is intended for drugs that target seriously debilitating or life threatening diseases for which an unmet medical need exists. The drug needs to have a positive benefit-risk balance and the benefit of immediate availability needs to outweigh the risks associated with the lack of comprehensive clinical evidence. A CMA is subject to requirements to conduct further studies after authorisation. Once comprehensive data are provided and the benefit-risk balance remains positive, a CMA can be converted into a standard marketing authorisation.[26]

Authorisation under exceptional circumstances (AEC)

AEC is a type of marketing authorisation that can be granted by the EMA for drugs for which comprehensive clinical or non-clinical data cannot be provided, such as for very rare diseases, because it is considered unethical to collect these data, or because the current state of scientific knowledge does not allow it. An AEC is also subject to requirements to conduct further studies after authorisation, but is not normally converted into a standard marketing authorisation.[27]

und Wirtschaftlichkeit im Gesundheitswesen. They each publish separate assessments, which can lead to differing conclusions. This study focuses only on G-BA's assessments because of their responsibility for final appraisals and the inclusion of orphan drugs in their evaluations (unlike Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen)[31]

- Agenzia Italiana del Farmaco (HTA agency of Italy)
- European Society for Medical Oncology (ESMO; developed the magnitude of clinical benefit scale for grading the added benefit of oncology drug-indication combinations)
- American Society of Clinical Oncology (ASCO; developed the value framework for grading the added benefit of oncology drug-indication combinations through net health benefit scores)
- Prescrire (French independent drug bulletin). Despite a seemingly different scope than the other organisations, Prescrire is internationally renowned for its high quality and comprehensive drug evaluations conducted collaboratively by a team of physicians and pharmacists. The outcomes of Prescrire's assessments play an important part in informing drug related decision making.[32 33]

After retrieving all oncology drugs and their initial indications that had been approved by the EMA between 1995 and 2020, three cohorts were formed in line with the three objectives of the study. The added benefit cohort included all added benefit ratings of the drug-indication combinations that were evaluated by at least one of the organisations listed above. To ensure that our study's findings were grounded in comparable evidence conducted near the EMA approval date, we excluded evaluations performed more than 1.5 years before or after the EMA approval date. This decision was made to limit potential discrepancies in the evaluations of added benefits owing to the availability of additional evidence over time. HTA organisations generally perform assessments within 1.5 years after EMA approval, which makes this timeframe appropriate for our study.[34 35] The decision to also exclude evaluations conducted more than 1.5 years before the EMA approval date was essential because there are differences in timelines between regulatory authorities in the US and Europe, and we included organisations from both regions in our study.

The second cohort, the revenue cohort, included all oncology drugs for which revenue data were available. The third cohort, the combined cohort, comprised all oncology drugs with at least three years of revenue data available that had been evaluated for added benefit by at least one organisation. We excluded all drugs with several initial indications or that received new indications before the end of follow-up, which was checked by comparing the initial and most recent European public assessment reports. This strategy ensured that the revenue data were correctly attributed to the indications on which the added benefit ratings were based, which is important because added benefit evaluations apply to drug-indication combinations, whereas revenue data are relevant at the product level.

Data collection

Added benefit evaluation reports were collected by following a standardised data extraction guide developed by FB and discussed with LTB and Rick Vreman to ensure consistent extraction of the ratings from each organisation (see supplementary materials box S1). Added benefit ratings relate to specific drug-indication combinations. When added benefit ratings were assigned to subindications (eg, specific subpopulations) of the initial indication, these were treated as distinct drug-indication combinations in the study cohort. All retrieved added benefit ratings were recategorised using a four point ranking scale to indicate negative or non-quantifiable, minor, substantial, or major added benefit (see table 1), based on previous work.[15 37]

We retrieved global revenue data up to 2020 from publicly available financial reports of pharmaceutical companies on the level of the brand names of the included drugs. When financial reports indicated that only revenues of major or bestselling products were disclosed, we inferred that products of that company with missing revenue data were minor or less successful

Table 1 | Reclassification of all possible added benefit ratings of included organisations into four point ranking scale

Added benefit	ICER	HAS	G-BA	AIFA	ESMO-MCBS	ASCO-VF	Prescrire
Negative or non-quantifiable added benefit	P/I=promising but inconclusive; I=insufficient; D=negative; C-=comparable or inferior; C=comparable	5=no or not quantified clinical added value	Non-quantifiable additional benefit; no additional benefit proven; less additional benefit	Not innovative	NA	≤0=no benefit*	Not acceptable; judgement reserved; nothing new
Minor added benefit	C+=comparable or incremental; C++=comparable or better	4=minor clinical added value	Minor additional benefit	Potential or conditional innovation	1=negligible benefit; 2=negligible benefit; C=moderate benefit	0-40=low benefit	Possibly helpful
Substantial added benefit	B=incremental; B+=incremental or better	2=considerable clinical added value; 3=moderate clinical added value	Considerable additional benefit	NA	3=moderate benefit; B=substantial benefit	40-45=intermediate benefit	Offers an advantage; a real advance
Major added benefit	A=superior	1=major clinical added value	Major additional benefit	Fully innovative	4=substantial benefit; 5=substantial benefit; A=substantial benefit	≥45=substantial benefit	Bravo

AIFA, Agenzia Italiana del Farmaco; ASCO-VF, Value Framework from the American Society of Clinical Oncology; ESMO-MCBS, magnitude of benefit scale from the European Society for Medical Oncology; G-BA, Gemeinsamer Bundesausschuss; HAS, Haute Autorité de Santé; ICER, Institute for Clinical and Economic Review; NA, not applicable.
*The scale of the ASCO-VF is continuous and possible net health benefit scores range from −20 to 180.[36]

and made a note of them. The impact of these missing products was studied in a sensitivity analysis. All revenue data were expressed in US dollars through historical exchange rates of the date that the fiscal year ended and were converted to 2020 values using historical consumer price indices.[38 39] We calculated yearly cumulative revenues for each individual drug, starting from the year in which revenues were first generated (year 1 after market entry).

To assess potential discrepancies between added benefit and revenue among different approval pathways of the EMA, we categorised the study cohorts based on approval type, including SMAs, CMAs, and AECs. Information about approval types was retrieved from the European Commission's Union Register of medicinal products for human use.[40]

All data collection was performed until 31 August 2021. Extraction of all data was performed by FB and validated by Jan-Willem Versteeg through independent extraction of a random sample of 10% of the study cohort. Additionally, our extraction of revenue data was further validated using a previously developed dataset consisting of revenue data from a selection of orphan drugs.[41]

Data analyses

Added benefit

To evaluate the obtained ratings of added benefit in the added benefit cohort, we used descriptive statistics. We also assessed the number of drug-indication combinations that were evaluated across several organisations. We did not consolidate multiple added benefit ratings for a specific drug-indication combination into a single rating. Instead, we performed the analyses based on all the extracted added benefit ratings to maintain proximity to the original data and preclude the risk of losing the valuable variation found across scores for individual drug-indication combinations.

Comparison of revenues to estimated R&D costs

We assessed cumulative revenues of the revenue cohort for a maximum of eight years after market entry, in line with the estimated remaining patent exclusivity period of 7-10 years after market approval.[42] We compared the cumulative revenues obtained for individual drugs with estimates of R&D costs of a single oncology drug to analyse the time required for cumulative revenues to equal (ie, offset) R&D costs. For this comparison, we used estimates from a study by Prasad and Mailankody in which the median risk adjusted R&D costs of a single oncology drug were estimated to be $684m (range $166m to $2060m, adjusted to 2020 values).[7] These estimates also include the costs of failure and are in line with other estimates quoted by the pharmaceutical industry.[3 43] Additionally, we conducted a sensitivity analysis using alternative R&D estimates reported by Prasad and Mailankody, which incorporated 7% opportunity costs (median $800m, range $215m to $2747m, adjusted to 2020 values).[7]

To account for missing revenue data, we conducted a sensitivity analysis that corrected for the drugs for which revenue data were not available because the company only disclosed revenues of its major or bestselling products. Taking a conservative approach, we assumed that these missing products did not offset the estimated R&D expenses during the follow-up period in our study, thereby lowering the proportion of drugs that offset R&D expenses.

Association between added benefit and revenues

We visualised the cumulative revenues for different levels of added benefit in the combined cohort using boxplots. We also performed a linear regression analysis to estimate the association between added benefit ratings of the included drugs and corresponding cumulative revenues three years after market entry. The three year cumulative revenue cut

off ensures an appropriate balance between sufficient market penetration and minimal data loss owing to more recently approved drugs, which was particularly important given the small sample size of the combined cohort (149 added benefit ratings of 43 drugs with corresponding revenue data).

We estimated the association between each individual added benefit rating and the revenue datapoint of the corresponding drug. When a drug had been evaluated across different organisations, its revenue datapoint was linked to several added benefit ratings. Using this approach, we preserved the original data because using the median or mean added benefit rating of a drug could have resulted in invalid results owing to the large variation in added benefit ratings for the same drug.

We performed the linear regression analysis in R (version 4.1.0) and RStudio (version 1.4.1717) and used the lm.cluster function of the miceadds package to incorporate a cluster effect in the analysis to correct for linking revenue datapoints to several added benefit ratings. We checked the assumptions of linear regression and evaluated the robustness of our estimates by removing outliers in a sensitivity analysis.

Subgroup analyses: standard versus expedited approvals

In a subgroup analysis of the added benefit cohort, we calculated risk ratios with 95% confidence intervals to evaluate the association between the EMA approval pathway and level of added benefit. To distinguish between added benefit and negative or non-quantifiable added benefit, we combined the ratings categorised as major, substantial, and minor added benefit.

We assessed whether cumulative revenues were higher for certain approval pathways in the revenue cohort. AECs were excluded from the analysis owing to their small numbers (n=6). Cumulative revenues five years after market entry (drugs with less than five years of revenue data available were excluded for this analysis) were compared between SMAs and CMAs by performing a Mann-Whitney U test, in which $P<0.05$ was considered statistically significant. A period of five years was chosen because this strikes an appropriate balance between a sufficiently long follow-up—surpassing the duration of most budget impact predictions by HTA agencies—and a follow-up short enough to ensure that none of the drugs would have patent expiration, which would hamper comparison of the cumulative revenues.[44]

Finally, we repeated the linear regression analysis in the combined cohort to estimate the association between added benefit ratings of the included drugs and corresponding cumulative revenues three years after market entry for different approval pathways. AECs were excluded because of their small numbers (n=2).

Patient and public involvement

Because of lack of funding, patients and members of the public were not involved in the design and conduct of this study. However, the authors plan to involve patient representatives during dissemination of the study findings.

Results

Study cohort

Figure 1 presents a flowchart of the inclusion process and the characteristics of the three distinct study cohorts. There were 131 oncology drugs with 166 indications which had been evaluated for their added benefit by at least one organisation within the required timeframe, yielding a total of 458 added benefit ratings (added benefit cohort). Revenue data were available for 109 drugs (revenue cohort), of which 43 were evaluated by at least one organisation, had at least three years of revenue data, and were associated with a single indication at the end of the follow-up period. A total of 149 added benefit ratings corresponded to these 43 drugs (combined cohort). Supplementary materials table S1 presents a more detailed overview of the characteristics of the drugs and drug-indication combinations in the respective study cohorts.

Added benefit

Of the acquired 458 added benefit ratings, 59 (13%) were classified as major benefit, 107 (23%) as substantial benefit, 103 (23%) as minor benefit, and 189 (41%) as negative or non-quantifiable benefit. The 166 drug-indication combinations included were most commonly assessed across one, two, or three organisations (n=39, 23%; n=41, 25%; n=33, 20%, respectively), whereas none of the drug-indication combinations were evaluated by all seven organisations. Supplementary materials table S2 presents the distribution of added benefit ratings for each organisation.

Comparison of revenues to estimated R&D costs

Figure 2 shows the median cumulative revenues of the revenue cohort from years 1 to 8 after market entry, and the estimated R&D costs (supplementary materials table S3 gives more details on the number of drugs available for yearly follow-up). The median cumulative revenues exceeded the minimum R&D costs of $166m within two years, the median R&D costs of $684m within three years, and the maximum R&D costs of $2060m within just over five years after market entry. Figure 3 (upper panel) shows the proportion of drugs that have offset the median estimated R&D costs of $684m for each year after market entry. Within eight years of market entry, 50 of 55 (91%) drugs surpassed the median R&D costs. In a sensitivity analysis that assessed the impact of missing data of minor or less successful drugs (fig 3, lower panel), a similar trend was found, and 50 of 61 (82%) drugs exceeded the median R&D costs within eight years. Supplementary materials table S3 presents more details on the number of drugs available for yearly follow-up. The sensitivity analysis that used alternative R&D estimates and included opportunity costs produced similar results to the main analysis (data not shown).

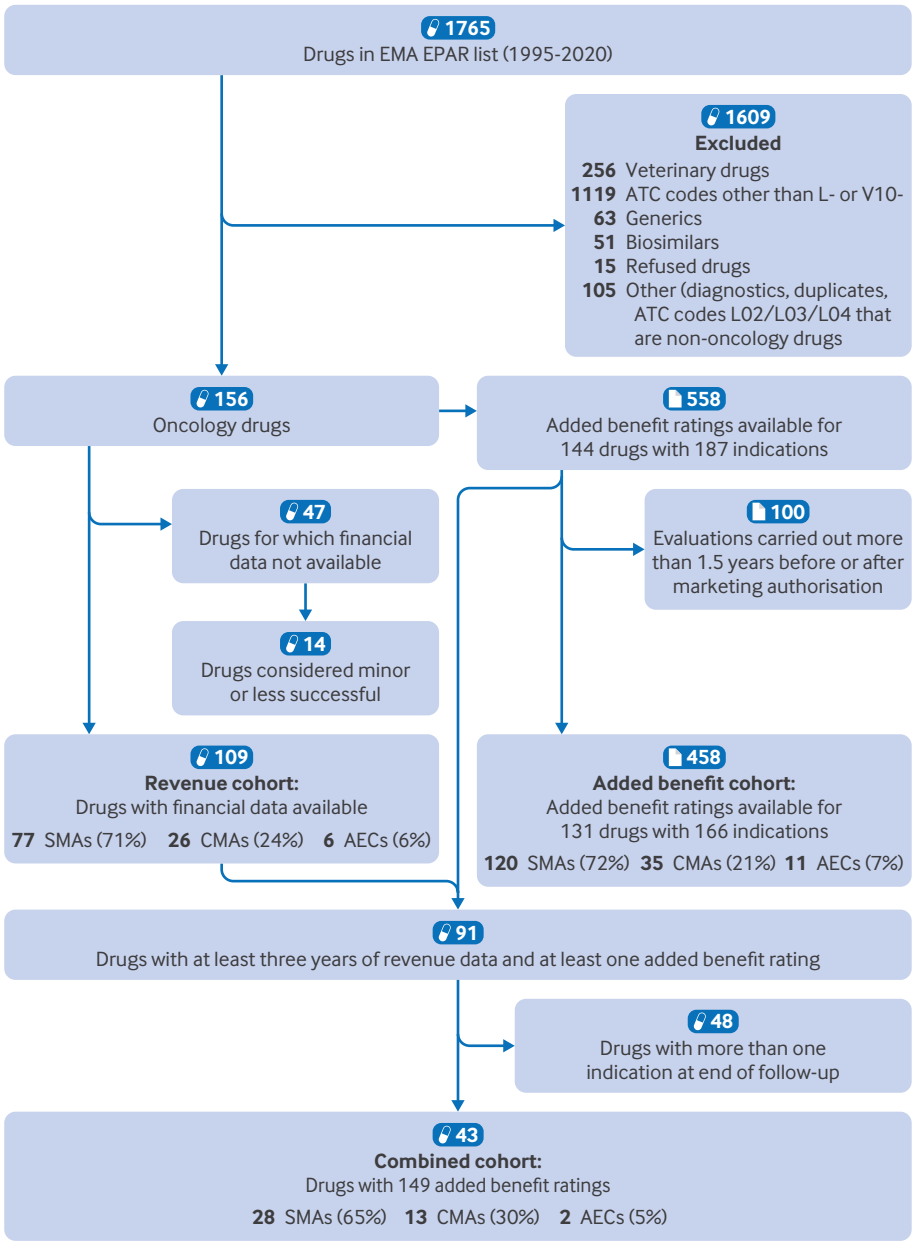

Fig 1 | Flowchart of inclusion process leading to three final study cohorts. Subgroup analyses were performed with SMAs, CMAs, and AECs in added benefit cohort, and with SMAs and CMAs in revenue cohort and combined cohort. AEC, authorisation under exceptional circumstances; ATC, Anatomical Therapeutic Chemical; CMA, conditional marketing authorisation; EMA, European Medicines Agency; EPAR, European public assessment report; SMA, standard marketing authorization

Association between added benefit and revenues

Figure 4 shows that cumulative revenues three years after market entry generally increased with the level of added benefit, although cumulative revenues varied, in particular for drugs with substantial and major added benefit. The linear regression analysis estimated that the median cumulative revenues three years after market entry for drugs with major and substantial added benefit were $502m and $506m higher than drugs without benefit, respectively. These results were not statistically significant, probably owing to the large variance and the relatively small sample size available for this analysis (149 added benefit ratings for 43 drugs). Supplementary materials table S4 gives more detailed results of the linear regression analysis.

Subgroup analyses: standard versus expedited approvals

Added benefit

Of the 341 added benefit ratings for drug-indication combinations approved through SMAs, 124 (36%) were classified as negative or non-quantifiable compared with 56 of 98 (57%) and 9 of 19 (47%) added benefit ratings for drug-indication combinations

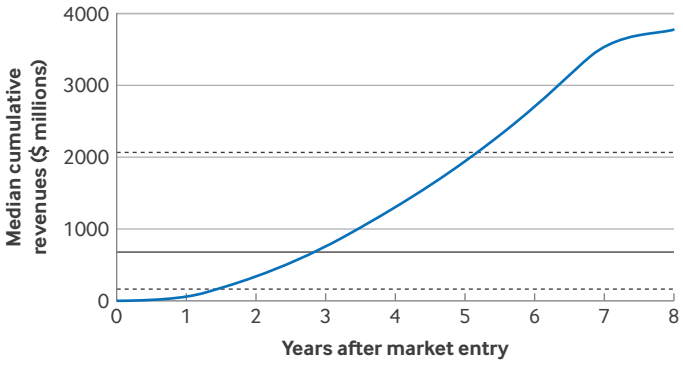

Fig 2 | Median cumulative revenues between years 1 and 8 after market entry. Dashed lines indicate estimated research and development (R&D) costs of a single oncology drug, with median of $684m (range $166m to $2060m; $1=£0.782, €0.88, adjusted to 2020 values). Number of drugs for which follow-up data were available ranged from 109 in first year to 55 in eighth year of study period

approved through CMAs and AECs, respectively. CMAs alone (risk ratio 1.57, 95% confidence interval 1.26 to 1.96) and in combination with AECs (1.53, 1.23 to 1.89) were more likely to receive a rating of negative or non-quantifiable added benefit compared with SMAs. AECs alone also had a point estimate greater than 1.0 for a negative added benefit rating, but owing to the small sample size, this should be interpreted with caution (see supplementary materials table S5).

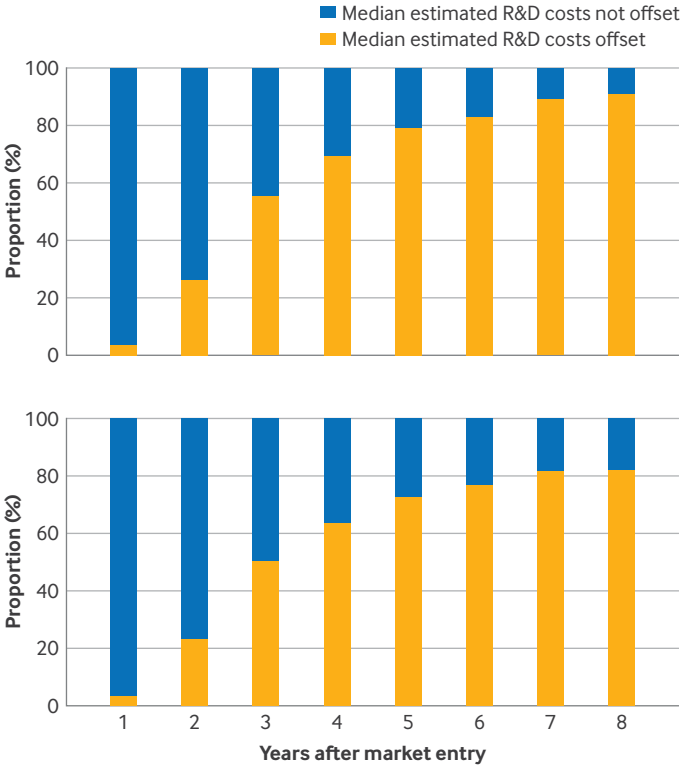

Fig 3 | Upper panel: proportions of drugs that offset median estimated research and development (R&D) costs of $684m over time ($1=£0.782, €0.88, adjusted to 2020 values). Number of drugs for which follow-up data were available ranged from 109 in first year to 55 in eighth year of study period. Lower panel: sensitivity analysis accounting for drugs with missing revenue data owing to selective disclosure of major or best selling products. Number of minor or less successful drugs ranged from 14 in first year to six in eighth year of study period

Comparison of revenues to estimated R&D costs

Cumulative revenues of CMAs were distinctly lower than those of SMAs (fig 5). Five years after market entry, the median cumulative revenues of CMAs (n=17) were $1105m lower compared with SMAs (n=58), or almost twice as low ($1196m *v* $2301m, respectively), although this difference was not statistically significant (P=0.07).

The median cumulative revenues exceeded the minimum R&D costs of $166m within two years for SMAs and CMAs, the median R&D costs of $684m within three years for SMAs and four years for CMAs, and the maximum R&D costs of $2060m within five years for SMAs and eight years for CMAs (fig 5). At the end of the eight year study period, 37 of 41 (90%) SMAs and 8 of 9 (89%) CMAs had offset the median R&D costs (see supplementary materials figure S1), and median cumulative revenues of SMAs (n=41) were more than $3bn higher than those of CMAs (n=9; $5306m *v* $2276m, respectively). The observed decline in median cumulative revenues for CMAs between years 6 and 7 can be attributed to the varying market durations of the included drugs. Supplementary materials table S3 presents more details on the number of drugs available for yearly follow-up.

Association between added benefit and revenues

Revenues increased similarly for SMAs and CMAs, along with higher levels of added benefit, although these associations were not statistically significant. The linear regression analysis estimated that the median cumulative revenues three years after market entry for drugs with major and substantial added benefit were $429m and $413m higher than for drugs without added benefit, respectively (see supplementary materials table S6).

Discussion

Our study showed that oncology drugs approved by the EMA between 1995 and 2020 were often found to provide little or no added benefit. Our results on revenues showed that the median time to offset the median estimated R&D costs of $684m was three years, and 50 of 55 (91%) of the included drugs had recovered these costs within eight years. We found that higher added benefit ratings were generally accompanied by greater revenues. Moreover, negative added benefit ratings were more common for drugs initially approved through CMA and AEC compared with SMA, and cumulative drug revenues were found to be distinctly lower for CMAs than for SMAs. Correspondingly, initial CMAs took longer to offset the median estimated R&D spending in comparison to SMAs (four years versus three years).

Despite claims from the pharmaceutical industry that high drug prices are necessary to sustain the costs of R&D, studies have found no correlation between drug prices and R&D expenses.[45] A recent study

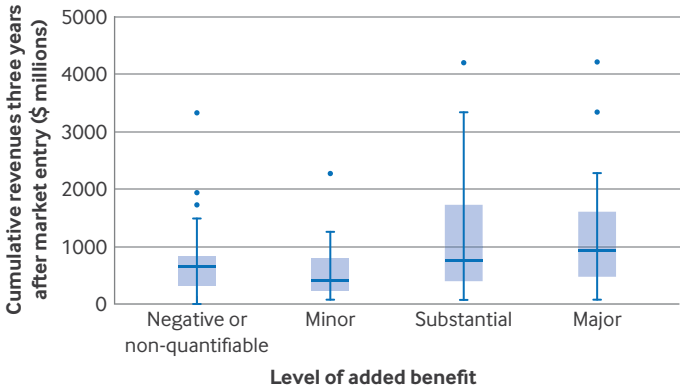

Fig 4 | Boxplots (median, maximum, minimum, upper and lower quartile) showing cumulative revenues three years after market entry for oncology drugs that received ratings of negative or non-quantifiable (n=50), minor (n=32), substantial (n=38), or major (n=29) added benefit (149 added benefit ratings for 43 drugs). Dots represent outliers. $1=£0.782, €0.88, adjusted to 2020 values

by Angelis and colleagues showed that the world's largest biopharmaceutical companies spent more on selling, general, and administrative activities than on R&D, with only 16-21% of revenues allocated to R&D between 1999 and 2018.[8] Additionally, Tay-Teo and colleagues found a median income return of $14.50 for every $1 spent on R&D costs.[46] Our findings complement these studies by showing that R&D costs are typically recovered within a few years of a drug's market entry, with the median time to recover the median and maximum estimated R&D costs being three and five years, respectively. Even for drugs with considerably lower added benefits at the time of initial approval (ie, CMAs), the median time to recover the median estimated R&D costs is four years (typically the timeframe within which more comprehensive evidence becomes available[21 47]).

Previous studies have extensively focused on the relation between added benefit and drug prices, in which no statistically significant associations were found.[2 14 23-25] However, drug prices might be an imperfect measure as they only reflect information for a single country and are often subject to confidential discounts; therefore, these findings should be interpreted with caution. Our study explores the association between added benefit and drug revenues. We view revenues as a more relevant measure because these hold global relevance and better reflect the earnings of a drug. Our findings imply that—irrespective of approval type—revenues of oncology drugs are generally in line with their added benefit, which is in concordance with our expectations.[2 14 23-25] This indicates that pharmaceutical companies might be incentivised to develop drugs with high levels of added benefit because these drugs are associated with higher revenues. However, we also observed that drugs with lower levels of added benefit were still able to recover their estimated R&D expenses within a relatively short time period. This finding indicates that while lower levels of added benefit might result in lower revenues, these are still sufficiently high to recover R&D expenses. Additionally, our results revealed a striking similarity in the revenues generated by drugs with substantial and major added benefits. These mechanisms in obtaining revenues might attenuate the potential incentive to develop high value drugs because pharmaceutical companies might be satisfied with the revenue generated from lower value drugs.

In subgroup analyses, we assessed whether added benefit and revenues were higher for certain approval types. CMAs and AECs are approval pathways intended for patients with unmet medical needs, for which the EMA determined that the benefit of immediate access outweighs the risks of increased uncertainty. Our results indicate that this potential to address unmet medical needs might be negated by the lack of comprehensive evidence inherent to these approval pathways, often resulting in negative added benefit ratings at the time of initial approval. Similarly, other studies found high numbers of negative added benefit ratings for expedited approval drugs.[15 18 21 22] All these findings imply that drugs approved through expedited pathways, which are meant to allow access to promising drugs, do not necessarily show an added benefit at the time of initial evaluation. Our study extends previous research by revealing that CMAs not only have more negative added benefit ratings than SMAs but also generate substantially lower revenues, and accordingly, take longer to offset estimated R&D costs. The median time to recover R&D expenses ranged between three and four years for SMAs and CMAs, respectively. Because CMA is a pathway that aims to speed up drug approval, it might also lead to earlier market entry and therefore an increased period of time to generate revenues before patent expiration. Conversion from CMA to SMA takes place once the marketing authorisation holder fulfils the obligation to provide more comprehensive evidence, a process that typically occurs within four years of receiving regulatory approval.[21 47] This conversion

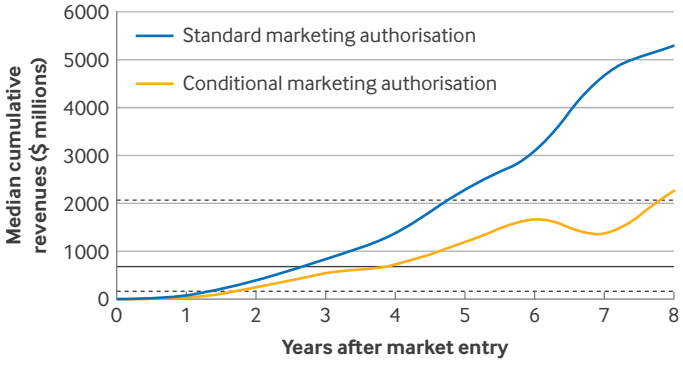

Fig 5 | Median cumulative revenues of oncology drugs approved through standard marketing authorisations (SMAs) and conditional marketing authorisations (CMAs) from years 1 to 8 after market entry. Dashed lines indicate estimated research and development (R&D) costs of a single oncology drug with median of $684m (range $166m to $2060m; $1=£0.782, €0.88, adjusted to 2020 values). Number of drugs in each year ranged from 77 for SMAs and 26 for CMAs in first year to 41 for SMAs and nine for CMAs in eighth year of study period because not all included drugs had been on the market for full study period

point can be considered the potential starting point for generating revenues by SMAs, coinciding with the approximate offsetting of R&D costs by initial CMAs. This prompts the question of whether it is desirable for CMAs to have already offset their estimated R&D costs at this particular stage. Nevertheless, the difficulties in showing added benefit during reimbursement processes might negate the effects gained through earlier regulatory approval, given that after eight years, the difference in the median cumulative revenues between CMAs and SMAs is more than $3bn.

Limitations of this study

This study has several limitations. We focused solely on the initial indications of the included oncology drugs and evaluated the added benefit that was based on data submitted for initial approval because this reflects the entry into the market. We did not assess how this benefit evolves over time, including potential new indications, because this fell beyond the scope of our study. Additionally, to avoid potential discrepancies resulting from additional evidence becoming available over time, we excluded evaluations performed more than 1.5 years after the EMA approval date from the added benefit cohort. However, because some organisations from the US (ICER and ASCO) follow timelines of the US Food and Drug Administration for drug approval, which are typically earlier than EMA approval dates, we also excluded evaluations conducted more than 1.5 years before EMA approval to ensure that our findings were based on comparable evidence. While it would have been more accurate to consider US Food and Drug Administration approval dates for ICER and ASCO assessments, we chose to focus on EMA approval dates for our study.

We obtained ratings of added benefit from seven different organisations, each using a distinct scoring system. To ensure consistency, we converted these scores to a four point rating scale; however, alternative categorisations might have been possible, which could have produced different outcomes. Nevertheless, we attempted to reduce the risk of disagreements by aligning our methods with those used in previous research from our group.

Some drugs in our dataset are used for several indications, including non-oncology indications. The revenue data that we obtained were attributed to the drugs in an oncology setting, whereas this might not have been fully the case. This approach did not impact the comparison of revenues to added benefit because these drugs were excluded from that analysis to ensure that the revenue data were correctly attributed to the indications on which the added benefit ratings were based. Nevertheless, this exclusion might have introduced a selection bias, potentially leaving out highly successful blockbuster drugs that are used for several indications and generate substantial revenues. Consequently, our estimation of revenues in this analysis might have been conservative, and the actual revenues associated with the included drugs are potentially higher than we report. Additionally, our analyses did not consider the size of patient populations in the included indications because these data were unavailable, even though they affect the revenue generated. Future research could focus on indication based analyses or account for the size of patient populations.

Finally, we used an estimate of $684m (range $166m to $2060m) to examine returns on R&D investments, which did not include opportunity costs. This estimate was derived from a study by Prasad and Mailankody, who also reported ranges of R&D costs that incorporated opportunity costs.[7] However, because our analysis focused on comparing revenues with R&D costs, we deemed it appropriate to use estimates excluding opportunity costs. In a sensitivity analysis incorporating a range with 7% opportunity costs, our findings remained similar. Additionally, we used the same range of R&D costs for all drugs in our study cohort, even though this number might not be applicable for every drug. For example, Prasad and Mailankody found that drugs receiving accelerated approval generally had lower R&D costs compared with those receiving regular approval.[7] This finding suggests that our analysis on R&D costs for CMAs might have taken a conservative approach, while in reality, the median R&D costs for the initial development of these drugs could potentially be offset sooner than our estimated four year timeframe. However, the R&D estimates we used are consistent with other estimates cited by the pharmaceutical industry, account for failed products, and are adjusted to 2020 values.

When interpreting our study's findings, it is important to consider a potential role of the phenomenon of me-too versus first-in-class drugs. First-in-class drugs rely on a novel pharmacological mechanism and might be more likely to receive positive added benefit ratings and enjoy lengthier periods of competition-free usage. Subsequent me-too drugs, sharing similar mechanisms of action and developed through sequential innovation, might not always offer major advantages over their predecessors, resulting in lower added benefit ratings.[48] Additionally, these drugs might generate fewer revenues because they split market share with the first-in-class drug. Future research could focus on exploring potential discrepancies in added benefit and revenues between first-in-class and later-in-class drugs.

Health policy implications of findings

Creating regulatory incentives to effectively promote development of the most effective drugs for patients with the greatest needs is complex. On the one hand, approval might be expedited because drugs are expected to address unmet medical needs, while on the other hand, they more frequently create difficulties showing added benefits, potentially leading to negative added benefit ratings and lower revenues. Further collaboration on the interface of regulation and reimbursement is therefore needed to explore opportunities to more appropriately incentivise development of the most beneficial drugs addressing

the most pressing unmet needs.[30] In this context, it is noteworthy that the proposals for the reformed EU pharmaceutical legislation contain a definition of high unmet medical need based on morbidity and mortality reductions, ranging from meaningful to substantial.[49 50] Our study's results align with and support this definition, enabling the accurate identification of treatments addressing the most critical needs. Connecting this definition to regulatory incentives, such as market exclusivity, becomes crucial in effectively fostering the development of these essential drugs. Our study further underscores that almost all oncology drugs, even those lacking added benefits, manage to recover their estimated R&D costs. Consequently, we strongly advocate for a more thorough understanding of added benefit assessments and expedited pathways by formulary committees and to investigate the apparent discrepancy between assessed added benefit and (extent of) appropriate use in clinical practice.

Further policy recommendations for improved alignment might include increased use of parallel joint scientific consultations between regulatory authorities and HTA agencies, a key element within the recently adopted EU HTA Regulation.[51] Differences in evidentiary requirements between the EMA and HTA bodies often lead to positive benefit-risk assessments but negative added benefit assessments.[13-16] Through parallel joint scientific consultations, alignment on evidence requirements and assessment criteria can be established. In the context of expedited approvals that are inherently associated with less comprehensive evidence, parallel joint scientific consultations can prove invaluable to adequately navigate HTA requirements and truly achieve expedited patient access.

Moreover, our findings about the recovery of R&D costs can inform pharmaceutical pricing strategies. Managed entry agreements, for example, extend beyond simple reimbursement decisions and are effective strategies to mitigate uncertainties.[52] Given that many oncology drugs generate substantial revenues despite providing minimal added benefit, managed entry agreements emerge as valuable tools to establish flexible payment structures that reflect the value (or the lack thereof) of drugs to patients. Building on this, improved price transparency is a critical prerequisite for managing drug costs and enhancing sustainable patient access, providing opportunities to shape fair pricing strategies and policies more effectively.[3] Our study's findings and subsequent policy recommendations should be further discussed in initiatives aiming to ensure equitable, sustainable, and affordable patient access to innovative and expensive drugs, such as Beneluxa, the Oslo Medicines Initiative, and WHO's Novel Pricing Platform,[53 54] or can be used as input to develop new initiatives in this critical domain.

Conclusion

Our study revealed that evaluations of oncology drugs frequently result in a conclusion of negative or non-quantifiable added benefit. This finding is especially true for drugs approved through expedited pathways that are intended for promising drugs, but are simultaneously associated with an inherent lack of comprehensive evidence, which indicates a misalignment between regulatory and reimbursement policies. Oncology drugs with higher levels of added benefit tend to generate higher revenues than drugs with less added benefit, potentially creating incentives for pharmaceutical companies to develop high value drugs. However, drugs with lower added benefits are often able to recover their estimated R&D costs within a few years. It is crucial for policy makers to assess whether the current regulatory and reimbursement incentives are properly structured to promote and facilitate the development of the most effective drugs for patients with the greatest needs.

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The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Web appendix: Supplementary materials