Clinical Benefit and Drug Revenues: a Retrospective Study of Oncology Drugs Approved Between 1995 and 2020

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22-12-2021

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List of abbreviations

AB	Added benefit
AEC	Authorization under exceptional circumstances
AIFA	Agenzia Italiana del farmaco
ASCO	American Society of Clinical Oncology
ASMR	Amélioration du service médical rendu
ATC	Anatomical Therapeutic Chemical
ATMP	Advanced therapy medicinal products
CAV	Clinical Added Value
CEA	Cost-effectiveness assessment
CI	Confidence interval
CMA	Conditional market authorization
CPI	Consumer Price Index
CTCA	Cancer Treatment Centers of America
EMA	European Medicine Agency
EPAR	European public assessment report
ESMO	European Society for Medical Oncology
EU	European Union
FDA	Food and Drug Administration
FIC	First-in-class
G-BA	Gemeinsame Bundesausschuss
HAS	Haute Autorité de Santé
HTA	Health Technology Assessment
ICER	Institute for Clinical and Economic Review
INN	International nonproprietary name
IQR	Interquartile range
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheit Wesen
LIC	Later-in-class
MCBS	Magnitude of Clinical Benefit Scale
NCI	National Cancer Institute
NHB	Net Health Benefit
ORR	Overall response rate
OS	Overall survival
PFS	Progression free survival
QoL	Quality of life
R&D	Research and development
REA	Relative effectiveness assessment
ROI	Return on investment
RR	Risk ratio
VF	Value framework

Abstract

Background: Evaluations of added benefit (AB) play an important role in assessing the value of novel (cancer) drugs, which is important as prices of cancer drugs have been shown to increase significantly over time. Furthermore, an increasing number of drugs is approved via e.g. expedited pathways that require less comprehensive evidence, making the estimates of AB uncertain and weak. As a result, questions arise whether novel cancer drugs provide sufficient AB to healthcare systems, and whether profits by the pharmaceutical industry are not excessive.

Objective: To investigate trends in AB and drug revenues of novel oncology drugs between 1995 – 2020, and explore the association between AB and revenues.

Methods: All oncology drugs approved by the EMA between 1995 – 2020 were included (*n* = 156). AB ratings (*n* = 458) closest to EMA approval were retrieved from seven organizations (HAS, G-BA, ICER, AIFA, Prescrire, ESMO and ASCO). Time trends were evaluated for the whole study cohort and for specific subgroups and overall differences in AB between the subgroups were statistically assessed by Risk Ratios (RRs). Revenue data was retrieved from 109 drugs and corrected for inflation. Median annual revenues were calculated for the whole study cohort, as well as cumulative revenues per product over time, which were compared to estimates of R&D costs. Median revenues between different subgroups and the association between AB and revenues were assessed using Mann-Whitney U tests and linear regression, respectively.

Results: 41% of all retrieved AB ratings were found to be negative. Non-regular approvals were more likely to be rated as having no AB compared to regular approvals (RR = 1.53, 95% confidence interval (CI) 1.23 – 1.89). Furthermore, median annual revenues have been fluctuating around $500 million since 2000. We found that estimated R&D costs ($794 million) are earned back within a few years, with 82% of the drugs having a positive return on investment (ROI) after six years. Drugs with curative intent generated significantly less revenues five years after market entry compared to non-curative drugs ($520 million for curative and $2069 million for non-curative, p = 0.031). Additionally, the rate of generating revenues was found to be independent of the approval period. Last, a significant association between AB and drug revenues was not found, however, numerical differences indicated drugs with major AB to generate higher revenues than drugs with no AB. A statistically significant result was found during a sensitivity analysis that only included products with one indication at the end of follow-up, in which the incremental step from no AB to both substantial AB and major AB resulted in an increase in cumulative revenue of $506 million (95% CI $125 million – $886 million) and $502 million (95% CI $89 million – $915 million), respectively.

Conclusion: We found that non-regular pathways do not necessarily lead to drugs that demonstrate more AB compared to regular approved drugs, even though such pathways are intended to facilitate access to promising drugs. Our findings emphasize that manufacturers should aim at developing drugs that actually address an unmet clinical need that are associated with strong clinical evidence of its effects. Furthermore, curative therapies generated significantly less revenues, implying that it is challenging to develop and market a successful curative cancer drug. Additionally, median annual revenues were found to stay constant over time and to be independent of approval periods, but more research is needed to explore how this reflects industry profits. Last, since we found numerical differences as well as statistically significant results during the sensitivity analysis that indicated drugs with higher AB to generate higher revenues, we advocate future research to extend this analysis with additional variables regarding drug characteristics or approval types.

Layman's summary

After a novel medicinal product has been developed and has successfully gone through all clinical trial phases, it must get approval by a regulatory agency in order to obtain a marketing authorization in a specific area. In Europe, marketing authorizations are provided by the European Commission based on a recommendation from the European Medicines Agency (EMA). After market authorization has been granted, the drug may be marketed in all EU member states. Subsequently, national decisions have to be made regarding the reimbursement of the drug, which is informed by the process of health technology assessment (HTA). HTA agencies evaluate the amount of added benefit (AB) that a novel drug has in comparison to the standard of care. Similar to HTA agencies, there are also other organizations that assess the value of drugs, such as the medical journal Prescrire and the oncological frameworks ASCO and ESMO. Evaluations of such agencies are important, since pharmaceutical expenditures are continuously increasing, causing healthcare financing to come under pressure. Quantifying the value of drugs can facilitate the access to cost-effective drugs, and on the other hand stimulate price negotiations for drugs that are not cost-effective. Furthermore, since an increasing number of (cancer) drugs is approved via i.e. expedited pathways that require less comprehensive research, questions begin to arise if novel (cancer) drugs still provide sufficient AB to healthcare systems.

This study aimed at investigating trends in AB ratings and revenues of novel oncology drugs that were approved between 1995 – 2020 by the EMA, with regard to the complete study cohort as well as for specific subgroups related to characteristics of the drugs or their corresponding approval pathways. Additionally, we explored the association between AB and drug revenues. Drug revenues were corrected for inflation.

We retrieved AB ratings (*n* = 458) closest to the date of EMA approval, provided by four HTA agencies (HAS, G-BA, ICER, AIFA), a medical journal (Prescrire), and two oncological frameworks (ESMO and ASCO). A large part of these ratings (41%) was classified as no or non-quantifiable AB, with approvals via non-regular pathways containing an even larger part of negative evaluations (56%); non-regular approvals were 1.53 times more likely to be rated as having no AB compared to regular approvals. Non-regular pathways are intended to facilitate access to promising drugs, however, they are also associated with less comprehensive evidence (e.g. small clinical trials), resulting in weak and uncertain estimates of AB. Our results emphasize the importance of not only developing a drug that addresses an unmet clinical need, but also one that is associated with strong clinical evidence of its effects.

Furthermore, we found that median annual revenues have been fluctuating around $500 million since 2000, meaning that annual earnings per product have not necessarily changed. Moreover, we found that the estimated R&D costs of a single cancer drug ($794 million) are generally earned back within a few years, with >80% of the drugs in our study cohort having generated more revenues than the estimated R&D costs within six years from market entry. Only in the case of curative vs non-curative drugs, we found a statistically significant difference between cumulative drug revenues five years from the moment of market entry, with curative drugs having generated significantly less revenues ($520 million for curative and $2069 million for non-curative). This finding implies that it might be more challenging to develop a successful curative cancer drug, however, the small sample size of curative drugs (*n* = 8) in comparison to non-curative drugs (*n* = 80) complicates drawing firm decisions. We therefore advocate future research to repeat this analysis with a larger sample size.

Moreover, we found the rate of generating revenues to be independent of the approval period, meaning that the rate of generating revenues after drug launch has not necessarily changed over time. Last, a statistically significant association between AB and drug revenues was not found, however, we did find numerical differences that indicated drugs classified as major AB to have generated more revenues than drugs with no AB three years after the moment of market entry. Furthermore, a sensitivity analysis that only included a subset of the study cohort did yield statistically significant results, indicating the incremental step from no AB to both substantial AB and major AB to result in an increase in cumulative revenues of $506 million and $502 million, respectively. These findings are in agreement with our hypothesis, as we expected drugs with higher AB to generate higher revenues.

This study is, to our knowledge, the first to explore the association of AB and drug revenues. Previous studies have already focused on the relation between AB and drug prices, however, drug prices are an imperfect measure because they are subject to confidential discounts, thus, they do not reflect what is actually paid by health systems. We therefore chose to focus on drug revenues rather than drug prices, since revenues are a more accurate measure of what is earned with a specific drug. Thus, we encourage future research to also focus on the association between drug revenues and AB and to complement our study by e.g. assessing a larger sample size or drugs for other therapeutic areas.

1. Introduction

Once market authorization of a novel drug has been obtained, decisions must be made on a national level regarding its reimbursement. In many countries, reimbursement decisions are informed by the process of health technology assessment (HTA), performed by HTA organizations. Part of the HTA process is to assess a drug on its added therapeutic benefit in order to determine how much additional value a novel drug has in comparison to alternative treatments. From a public health perspective, the value of novel drugs lies in the therapeutic benefits that they have with respect to patients or society, such as survival gains or improved quality of life (QoL). HTA evaluations are typically based on predefined key principles and decision criteria, and consist of at least relative effectiveness assessments (REAs), but may also entail cost-effectiveness assessments (CEAs) and budget impact analyses (1–5). Most HTA organizations publish their assessments on added benefit (AB) in combination with a final appraisal, which is a translation of the factual evidence of REAs (and sometimes CEAs) into a rating (3). These appraisals are subject to a context-specific interpretation of the factual assessments in the light of regional or national preferences. Therefore, appraisals can differ considerably among countries and cannot easily be shared across jurisdictions (3,6).

Findings of HTA agencies are important in order to prioritize healthcare resources; products with high AB at a favourable price should be made easily accessible. Products that have poor value for money, on the other hand, ought to be prioritized for price negotiations (2). Prioritization is becoming increasingly important, since healthcare financing has come under pressure recent years due to increasing volumes and prices of innovative drugs. The enormous increase in pharmaceutical expenditures is in particular caused by – but not limited to – drugs for cancer, for which global spending reached $167 billion in 2020, and is estimated to reach $269 billion by 2025 (7–10). The high prices of oncology drugs are often justified by the need to finance research and development, as R&D costs are estimated to be $794 million for a single cancer drug (range $219 million – $2827 million) (11). However, a study showed that total R&D spending of a study cohort with ten cancer drugs equalled $9 billion, whereas total revenue after a median time of four years after approval was $67 billion; 7-fold higher than the corresponding R&D costs (11).

Furthermore, prices of cancer drugs have been increasing at a rate that strongly outpaces inflation, even if evidence emerges that the drug is less effective than initially believed (7,12,13). Simultaneously, novel approval pathways that require less comprehensive evidence (e.g. conditional marketing authorizations) and an increase in the approval of orphan drugs with small clinical trials lead to less certainty at the time of initial reimbursement decisions. Additionally, the approval of novel cancer drugs is often based on surrogate endpoints, making the estimates of AB uncertain (7,14,15).

As a result, there is a growing concern among stakeholders that drug prices are not in line with the demonstrated benefit of new oncology drugs. Hence, questions arise whether these drugs still provide sufficient AB to healthcare systems, and whether pharmaceutical industry profits are not excessive (8,9,12).

Costs and AB of (oncology) drugs have been the topic of scientific studies numerous times. Previous studies have already explored the relation between drug prices and AB. No significant association has been found (7–9,14,16,17). However, public list prices are an imperfect measure, because many drugs are subject to confidential discounts negotiated by hospitals, insurers, governments, and/or HTA organizations (8,9). Thus, these prices do not reflect what is actually paid by health systems. Additionally, each country has its own approach to drug pricing, making the prices of drugs heavily depend on a government's willingness (and ability) to pay (12,18). For example, countries in Europe have policies that allow their authorities to directly negotiate with pharmaceutical companies on drug prices, whereas the USA makes use of a decentralized decision-making process (1,7,16). As a result, prices of drugs are often higher when the drug is launched in the USA compared to the EU. However, also in Europe, the regulation of drug pricing varies per country, resulting in considerable price differences among countries (16). The present study therefore focused on drug revenues instead of drug prices, since revenues are a more accurate measure of what is earned with a drug.

Apart from AB assessments carried out by HTA agencies, there are other organizations that likewise assess the AB of (oncology) drugs. First, the French organization Prescrire publishes a monthly medical journal that addresses developments in the pharmaceutical industry, as well as evaluations of AB of new drugs (19). Second, the European Society for Medical Oncology (ESMO) and the American Society of Clinical Oncology (ASCO) have developed frameworks that can be used to evaluate the AB of oncology drugs (20,21). The two frameworks were initially developed to serve different purposes; the ESMO Magnitude of Benefit Scale (MCBS) was designed to identify high-priority oncology drugs that should be made rapidly available in every EU country. The ASCO Value Framework (VF), on the other hand, is more patient-oriented and aims to facilitate shared decision-making of physicians and patients about treatment options (7).

The objective of this study was to assess how AB ratings and revenues of novel oncology drugs have changed over time. Furthermore, we explored the relation between AB of oncology drugs and corresponding revenues. Additionally, differences in AB ratings and revenues were analyzed for

specific subgroups related to characteristics of the drugs or their corresponding approval pathways. In summary, the main objectives of the study were:

i. Examine how AB ratings of novel oncology drugs have developed over time (between 1995 – 2020);
ii. Investigate trends of AB ratings between subgroups of the study cohort;
iii. Explore how drug revenues of novel oncology drugs have developed over time (between 1995 – 2020);
iv. Examine trends of revenues between subgroups of the study cohort;
v. Investigate the association between AB and corresponding drug revenues.

2. Methods

2.1 Identification of the study cohort

All oncology drugs that have been approved in the EU since the inception of the EMA in 1995 up until 2020 were included. These were obtained through an Excel file of all European public assessment reports (EPARs) that is available on the website of the EMA (22). Veterinary drugs, generics, biosimilars and refused drugs were excluded from the dataset of the present study. Furthermore, all drugs with an ATC code starting with anything other than L- (antineoplastic and immunomodulating agents) or V10X- (radiopharmaceuticals for cancer treatments) were excluded (23). Last, the full list was manually checked to remove any diagnostics and non-oncology drugs.

Through the EPARs, the initial indications of the drugs (for which market authorization was granted by the EMA) were obtained. We only took the initial, oncolytic, indication(s) into account, meaning that novel indications for existing treatments were not included. If a drug had multiple initial oncolytic indications, the drug was included in the dataset separately for each indication. This is important because evaluations of AB are performed on the indication level – thus, a drug with multiple indications can have multiple AB scores (one for each indication). The dataset was therefore arranged in such a manner that every entry represented a unique indication of a drug.

AB was quantified using ratings of novel drugs assigned by four HTA organizations, a medical journal, and two frameworks of oncology societies: Haute Autorité de Santé (HAS, HTA of France), Gemeinsamer Bundesausschuss (G-BA, HTA of Germany), Institute for Clinical and Economic Review (ICER, HTA in the United States), Agenzia Italiana del Farmaco (AIFA, HTA of Italy), Prescrire, ESMO-MCBS and ASCO-VF. In the remainder of this report, the word *agencies* will be used for convenience as a collective name for the included organizations and frameworks. These specific agencies were chosen since their assessment reports are publicly available and written in a language that the authors could easily understand. Additionally, they utilize a multiple-point scale for assigning levels of AB, instead of solely publishing a decision on coverage. The AB ratings that were extracted do not include costs or cost-effectiveness. In Table S1 (Annex I), the key objectives and applied levels of AB of all agencies are summarized.

Since our study focused on two topics, AB and revenues, we are dealing with two distinct study cohorts. Note that AB ratings are provided on the indication level, whereas financial data applies to a drug product as a whole. Therefore, we will refer to *indications* during the AB analyses, whereas we will refer to *drugs* when addressing financial data. Regarding the AB analyses, the final inclusion set consisted of all oncolytic indications that were evaluated by at least one of the agencies. Last, with

respect to the revenue analyses, the final inclusion set comprised all oncolytic drugs from which revenue data were available. We will refer to these as the AB study cohort and the revenue study cohort, respectively.

2.2 Data extraction

2.2.1 Added benefit ratings

For the quantification of AB, we focused on the first available assessments of the included drugs for each of the agencies – that is, the assessment that is closest to the date of market authorization. Since we included seven evaluating agencies, there were often multiple AB ratings associated with an individual indication. Re-assessments were not taken into account. Moreover, as mentioned before, AB assessments are carried out for a specific indication of an individual drug. In a few cases, an agency subdivided an indication in multiple types; for example, a different evaluation (and subsequently, a different rating) was provided for the drug used in first-line treatment, compared to second- or third-line treatment. The entry in question was then duplicated in the dataset, and the indications were specified for each subtype. If other agencies did not use the same extent of specification, it was assumed that the allocated ratings were applicable to all subtypes of the indication in question. More details on this approach can be found in Annex II.

A data extraction guide was developed to consistently extract the AB scores of each agency (Annex II). Note that not all drugs in the study cohort were evaluated by each of the included agencies, which can either be because agencies chose not to evaluate every drug, or because their scoring method is not applicable to all types of drugs. The ESMO and ASCO frameworks, for example, have not been validated for the assessment of drugs for haematological malignancies (5,24). Additionally, agencies have not always been transparent about their evaluations, meaning that not all evaluations are publicly available. During data extraction, the dates of all evaluation reports were documented. When time passes, additional clinical evidence could become available, which might lead to a different judgement of AB. Therefore, we excluded evaluations from the AB study cohort that were carried out more than 1.5 years after (or 1.5 years prior to, in the case of ASCO and ICER) market authorization by the EMA. This timeframe was chosen because it is in general the period within HTA organizations that we included evaluate drugs (25). AB ratings were collected up until the 31st of August 2021.

2.2.2 Revenues

For all included drugs, we retrieved revenues or sales from publicly available financial reports of pharmaceutical companies, complementing a database supplied by the authors of a previous study

(26). This was done on the level of the brand name of the products. Since individual products are sometimes marketed by various companies, it was first mapped out which companies market which products. Financial reports of all drugs were retrieved since their first year of generating revenues up to the most recently published annual report that was available. For each company, it was documented what type of finances were reported (sales or revenues) and when the fiscal year ended. Note that revenues and sales are always reported for a product as a whole, even if it is used for multiple indications, as opposed to AB ratings, which are assigned on the level of individual indications.

We could not retrieve revenue data of all drugs in our study cohort, partly because some financial reports were not available, but also due to some companies only reporting financial data of their major or best-selling products. We made a note of the drugs of which financial data was missing due to this reason, as we assume these to be minor products that cause our estimate of the median revenues to turn out higher than the exact revenues (see Annex V). We will refer to these as *missing minor products*.

2.3 Data categorisation

2.3.1 Assignment of subgroups

The drugs and indications included in the study cohorts were categorized in subgroups, based on characteristics of the drugs or their approval pathway. In Annex III, it is specified how the subgroups are defined and how they were assigned, including our hypotheses regarding AB. Note that all subgroups were applied to the time of initial approval. The subgroups that were included are;

- Approval type: regular vs non-regular approvals (the latter including conditional market authorizations (CMAs) and authorizations under exceptional circumstances (AECs));
- Innovation level: first-in-class vs later-in-class drugs;
- Orphan status: orphan drugs vs non-orphan drugs;
- Malignancy type: drugs for solid vs drugs for haematological malignancies;
- Therapy intent: curative vs non-curative drugs;
- Availability of alternatives: alternative treatments available yes/no;
- Therapy type;
    - ATMP vs non-ATMPs;
    - Targeted vs non-targeted therapies.

2.3.2 Added benefit ratings

As can be seen from Table S1 (Annex I), each of the agencies use their own, unique scale to indicate the level of AB. However, to be able to analyze the results, all ratings must lie on the same scale.

Therefore, we re-categorized all acquired ratings to our own 4-point scale of AB, indicating no/non-quantifiable, minor, substantial, or major benefit, as is shown in Annex IV (Table S2). We chose not to average ratings to end up with a single rating per indication, but rather used all acquired ratings for the analysis.

2.3.3 Revenues

All acquired revenues and sales data were expressed in US dollars. Conversion of currencies was performed using historical exchange rates of the date that the fiscal year ended (27). All amounts in dollar were then corrected for inflation using historical Consumer Price Indices (CPIs), which is important since we are dealing with a relatively large time frame; the cumulative rate of inflation of 1995 compared to 2020 is 69.8% (28,29). For each year, the revenues of all oncology drugs in that year were summed, giving an indication of the total revenues within the oncology field. Also, for each drug, revenues were summed over time, giving cumulative revenues per drug over the years since its introduction.

2.4 Data analysis

We performed eight analyses, which correspond to the study objectives mentioned in the introduction. Four analyses related to AB. Note that the ESMO-MCBS and ASCO-VF make use of exclusively positive scales, hence, any assigned score corresponds with some extent of AB. To verify if this did not influence our main analysis (analysis 1), we also analyzed the ratings of the HTA agencies and Prescrire (analysis 2) apart from the ESMO and ASCO ratings (analysis 3). Last, we analyzed the ratings of each agency individually (analysis 4). The remaining analyses are related to revenues (analyses 5 – 7), and the last analysis assessed the relation between AB and revenues (analysis 8). The majority of the analyses were also performed for the listed subgroups. Note that we considered several different time periods for the individual analyses. The rationales behind these are discussed below. In short, the following analyses were performed (specifications are provided in sections 2.4.1 – 2.4.3):

<u>Added benefit</u>

1. AB ratings of whole study cohort over time;
2. AB ratings of HTA agencies and Prescrire over time;
3. AB ratings of ESMO and ASCO over time;
4. AB ratings of individual agencies over time;

<u>Revenues</u>

5. General trend of the whole study cohort over time (cumulative, mean and median annual revenues);

6. Median cumulative revenues with interquartile range (IQR) of whole study cohort over time;
7. First five years of generating revenues for different approval periods;

Relation added benefit and revenues

8. Association AB and corresponding drug revenues.

2.4.1 Added benefit

Regarding AB, four analyses were performed. The main analysis entails the ratings of the whole study cohort over time. In the second and third analyses, the cohort was split in two, with the first cohort containing the ratings of the HTA agencies and Prescrire, whereas the second includes the ratings of the ESMO and ASCO frameworks. The ratings were plotted in separate figures to observe temporal trends. These analyses were repeated on the subgroup level. Decomposing the overall trend in subgroups is important, since analyzing all acquired data at once allows opposite trends to cancel each other out. In the fourth analysis, the acquired ratings were evaluated for individual agencies. A subgroup analysis was also performed for each agency.

With regard to the subgroup analyses, Risk Ratios (RRs) with 95% CIs were calculated to assess the relationship between characteristics of the subgroup and the level of AB, in which $p < .05$ was considered statistically significant. For the sake of the analyses, we only distinguished between 'no AB' and 'AB', the latter including the categories major, substantial, and minor AB. Regarding the subgroup analysis of only the ESMO-MCBS and ASCO-NHB ratings, we distinguished between 'low AB' (minor AB) and 'high AB' (substantial and major AB), since these scales inherently suggest an AB. Last, note that some subgroups only contain a small number of indications. We therefore established a sample size threshold of > 5 AB ratings in each subgroup for assessing time trends.

2.4.2 Revenues

Regarding revenues, three analyses were performed. First, the general trend in the oncology field over time was observed by summing the revenues of all oncology drugs in each year. Additionally, the mean and median revenues per product were calculated for each year. In the second analysis, revenues from each drug were summed up over time, resulting in cumulative revenues for all drugs. These data was then normalized to indicate cumulative revenues from the year in which first revenues were generated as year 1, which we will refer to as the *moment of market entry*. Then, median cumulative revenues including IQRs of the whole study cohort were calculated for each year since the moment of market entry. This was analyzed for the full study period (year 1 – year 20), as well as concentrated on year 1 – 8 to get more insight in the first few years after market entry. Furthermore, this time frame lies within the estimated remaining patent exclusivity period of 7 to 10 years after market approval (30).

We compared the obtained cumulative revenues to the estimated R&D costs of a cancer drug, in order to analyze how long it approximately takes before cumulative revenues equal R&D costs. We used estimates of a 2017 study in which the median risk-adjusted R&D costs were estimated to be $794 million (range $219 million – $2827 million) (11). These values also include the costs of failure and are comparable with other estimates quoted by the pharmaceutical industry (12,31). We analyzed the number of drugs that had generated more revenues than the median- and maximum R&D costs for each year, in which we consider a drug to have a positive return on investments (ROI) when it has generated more revenues than the median R&D costs of $794 million. We corrected for missing revenue data of minor products by including these products in the total number of drugs per year, while taking the approval years of the minor products in consideration. For example, minor products (with no revenue data available) approved in 2018 have been generating revenues for three years and were thus included in the total number of drugs in year 1 – 3. We assumed that these drugs did not generate more than R&D costs in any of the years, as this is the most conservative approach. Annex V entails an elaboration on the missing revenue data, including the missing minor products.

Previous analysis was repeated on the subgroup level. Here, the following subgroups were assessed; approval type, innovation level, orphan status, therapy intent, and availability of alternatives. The other subgroups were not taken into account because no differences in revenues were expected within those groups. Median cumulative revenues at year 5 were compared within each subgroup by performing Mann-Whitney U tests, in which $p < .05$ was considered statistically significant. A period of five years was chosen, as this is shorter than the usual remaining patent exclusivity period and in line with the projections of HTA agencies, that usually predict budget impact and market penetration up to three to five years after market entry (32).

Third, the rate of gaining revenues in the first five years from the moment of market entry was analyzed, and graphically compared between time intervals. A period of five years was chosen due to the same reason described above. To compare time intervals, the study cohort was split in five categories that represent the different approval periods (1995 – 2000; 2001 – 2005; 2006 – 2010; 2011 – 2015; 2016 – 2020). Median cumulative revenues of each year were calculated for all categories.

2.4.3 Relation added benefit and revenues

Last, we performed linear regression analyses in order to estimate the association between AB ratings of the included drugs and corresponding cumulative revenues three years from the moment of market entry, i.e. the difference in cumulative revenue per stepwise increase in AB rating, with $p < .05$ being considered statistically significant. We did not add any product characteristics in the model as

covariates. Since AB ratings are assigned on the indication level, and drug revenues on the product level, we attributed revenues of a single product to the corresponding indications. Thus, revenues of a product with e.g. two indications were associated with corresponding revenues two times. The analysis was performed for the whole study cohort, as well as for individual agencies. We chose three years after the moment of market entry in order to limit data loss (i.e. drugs that have been launched in the past few years), and because this is in accordance with predictions of budget impact and market penetration. Our hypothesis is that drug revenues are in line with AB, i.e. we expect drugs with higher AB to have generated significantly higher revenues.

Last, we performed a sensitivity analysis in which only the drugs were included that had one indication at the end of follow-up (31st of August, 2021). With this new cohort, the association between AB and cumulative revenues at year 3 was evaluated in the same manner as described above.

3. Results

3.1 Study cohort

A flowchart of the inclusion process is shown in Figure 1. As can be seen, 156 oncology drugs remained after the exclusion process. Of this selection, financial data was available of 109 drugs (70%), constituting the revenue study cohort. Table S3 (Annex V) shows an overview of the drugs with missing revenue data, of which 14 products were missing while it was specifically stated in the financial report that only major or best-selling products were reported. These drugs were thus considered as *missing minor products*. The final AB study cohort consisted of 458 AB ratings of 130 drugs (83%) and 166 indications. Furthermore, there were 90 drugs of which both revenue data and at least one AB rating was available, constituting the AB + revenue cohort. Of these, 70 (79%) had only one initial indication, and 45 (50%) had only one indication at the end of follow-up. Table 1 describes the characteristics of the 166 indications in the AB study cohort and the 109 drugs included in the revenue study cohort. Information on the distribution of both cohorts among the included subgroups can also be found in this table.

Table 1: Characteristics of the included indications (*n* = 166) and drugs (*n* = 109) for the AB cohort and revenue cohort, respectively. Note that all characteristics are based on the indication/drug at the time of initial approval.

Characteristic	AB cohort: No. of indications (%)	Revenue cohort: No. of drugs (%)
Disease site*		
Blood	60 (36)	38 (35)
Breast	20 (12)	15 (14)
Gastrointestinal	12 (7)	10 (9)
Genitourinary	19 (11)	15 (14)
Gynaecologic	6 (4)	4 (4)
Lung	21 (13)	14 (13)
Other	10 (6)	9 (8)
Skin	15 (9)	11 (10)
Thyroid	3 (2)	2 (2)
Approval year		
1995 – 2000	4 (2)	8 (7)
2001 – 2005	12 (7)	10 (9)
2006 – 2010	27 (16)	16 (15)
2011 – 2015	54 (33)	35 (32)
2016 – 2020	69 (42)	40 (37)
Approval pathway‡		
Conditional approval	35 (21)	26 (24)
Exceptional circumstances	11 (7)	6 (6)
Regular	120 (72)	77 (71)

Accelerated assessment		
Yes	14 (8)	10 (9)
No	152 (92)	99 (91)
Orphan designation		
Yes	68 (41)	46 (42)
No	98 (59)	63 (58)
Innovation level		
First-in-class	62 (37)	41 (38)
Later-in-class	104 (63)	68 (62)
Therapy type†		
ATMPs	4 (2)	4 (4)
Chemotherapy	29 (16)	20 (18)
Hormone therapy	3 (2)	4 (4)
Immunotherapy	41 (25)	31 (28)
Other	3 (2)	3 (3)
Targeted therapy	142 (86)	91 (83)
Malignancy type*		
Haematologic cancer	59 (36)	38 (35)
Solid cancer	107 (64)	72 (66)
Therapy intent		
Curative	14 (8)	9 (8)
Non-curative	152 (92)	100 (92)
Alternative treatments available		
Yes	101 (61)	67 (61)
No	56 (34)	31 (28)
Under some circumstances§	9 (5)	11 (10)

* drugs of the revenue cohort may qualify for more than one category;

† drugs and indications of both cohorts may qualify for more than one category;

‡ all approval types are mutually exclusive, except for accelerated assessment;

§ i.e. only regarding a subset of the patient group. In the revenue cohort, it could occur that alternatives are only available for one of the indications.

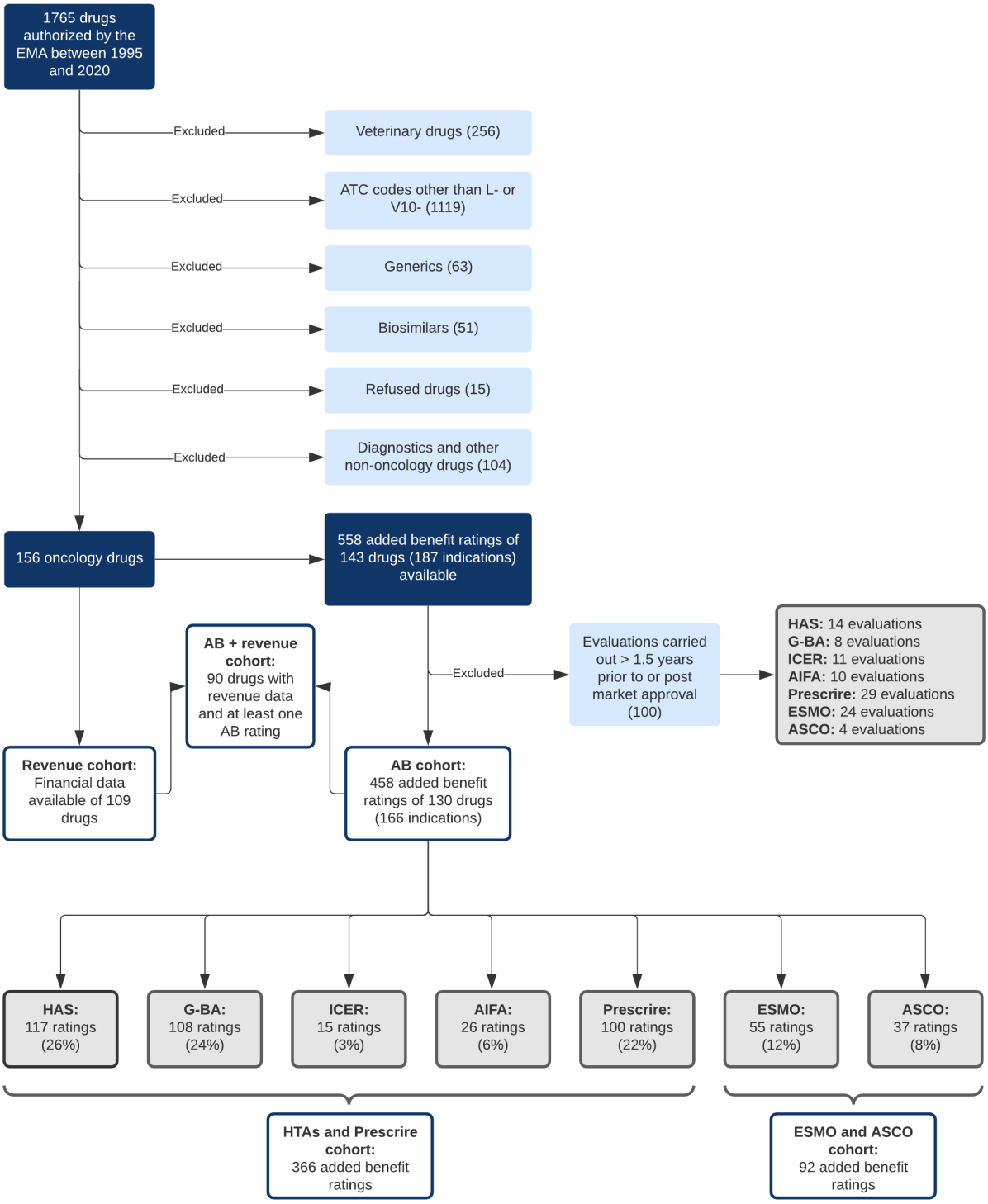


Figure 1: Flowchart of the inclusion process, in which three separate study cohorts were constituted (revenue cohort, AB cohort, and AB + revenue cohort). The AB cohort was subsequently split in two.

3.2 Added benefit

3.2.1 Ratings of complete study cohort

In Figure 2, specifications are provided on the acquired ratings of each agency, including the distribution among the four possible levels of AB. Overall, 59 (13%) ratings were classified as major benefit, 107 (23%) as substantial benefit, 103 (22%) as minor benefit, and 189 (41%) as no/non-quantifiable benefit. In the case of HAS, G-BA, and Prescrire, the majority of the AB ratings were classified as no/non-quantifiable benefit, whereas the ratings of AIFA and ASCO were primarily classified as major benefit. Last, the ratings of ESMO and ICER were predominantly categorized as substantial benefit. Figure 2 shows that all ratings of the ESMO and ASCO represent some extent of AB, which is why these frameworks were also analyzed separately from the other agencies. Furthermore, a scatterplot that contains the AB ratings of all included agencies is shown in Figure 3. In this plot, the temporal trend of AB ratings can be observed, which shows that the number of ratings of all levels of AB has been increasing over time.

Next, the distribution of AB ratings among the included subgroups is shown in Figure 4. RRs were calculated to examine the association between AB and each characteristic of the subgroups (Table 2). A significant association was only found between approval type and AB, with RR 1.53 (95% CI 1.23 – 1.89, $p < .001$). Non-regular approved indications were thus more likely to be evaluated as having no AB. The trend in AB ratings over time in this specific subgroup is displayed in Figure 5. Of the AB ratings, 341 evaluations were classified as regular approvals, compared to 117 non-regular approvals. Figure 5 indicates that non-regular approvals were not often rated as having major benefit; this was only the case for nine evaluations (8%). Of the regular approved indications, on the other hand, 50 evaluations (15%) were classified as major benefit. Furthermore, 65 evaluations (56%) were rated as no/non-quantifiable AB in the non-regular subgroup, compared to 124 (36%) in the regular subgroup. Figure 5 shows that since 2012 indications with non-regular approvals are primarily and increasingly being rated as having no/non-quantifiable AB. The distribution of regular approvals on the other hand, is quite constant amongst the four levels of AB over the years. No clear time trends were observed in any of the other subgroups (see Annex VI).

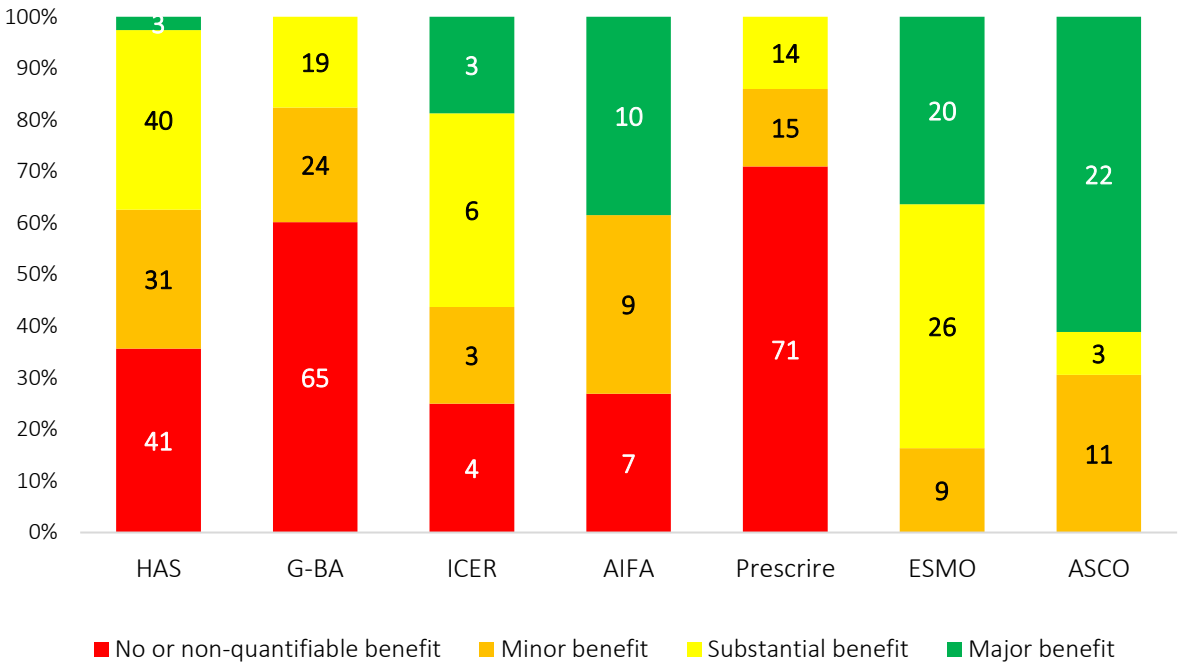


Figure 2: Distribution of AB ratings among the levels of AB for the included agencies.

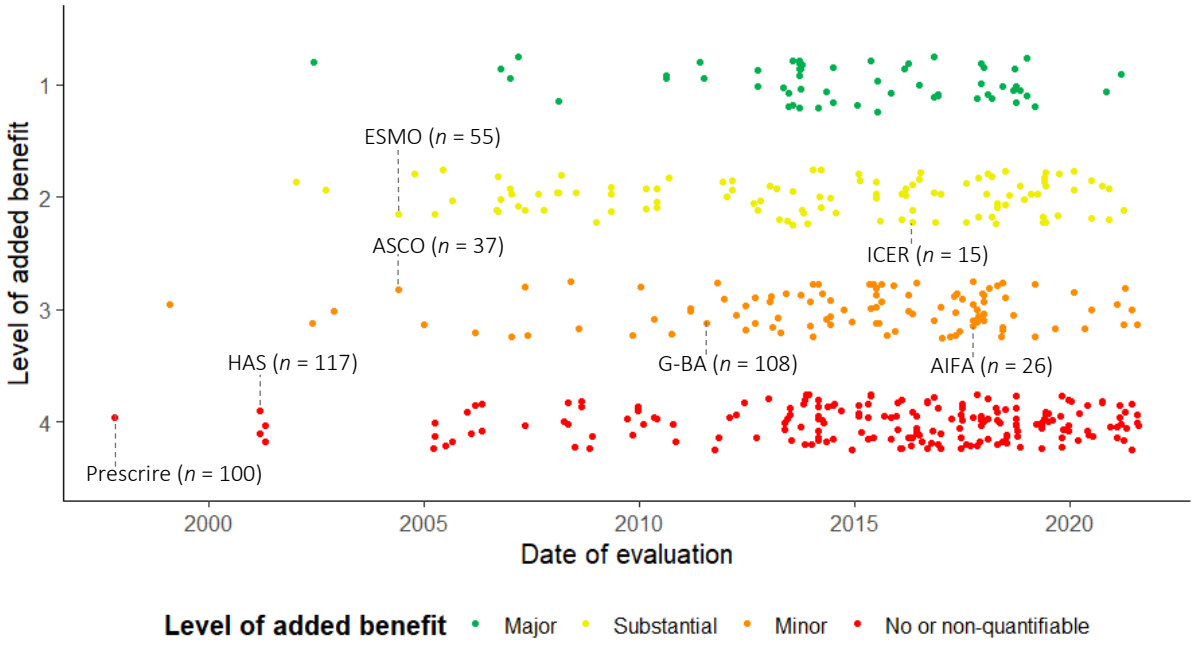


Figure 3: Scatterplot with all retrieved AB ratings (*n* = 458) over time. For each agency, the first rating that was retrieved is indicated with a dotted line. Date of evaluation refers to the date of AB evaluation.

Figure 4: Overall distribution of the AB ratings in the subgroups among the four levels of AB.

Table 2: Risk ratios of the included subgroups.

Subgroup	AB	No AB	Proportion no AB	Risk ratio	95% CI
Non-regular approvals	52	65	0.56	1.53	[1.23 – 1.89]
Regular approvals	217	124	0.36		
FIC	95	75	0.44	1.11	[0.89 – 1.39]
LIC	174	114	0.40		
Orphan	99	76	0.43	1.09	[0.87 – 1.36]
Non-orphan	170	113	0.40		

Solid	203	130	0.39	0.83	[0.66 – 1.04]
Haematologic	66	59	0.47		
Curative	12	12	0.50	1.23	[0.81 – 1.86]
Non-curative	257	177	0.41		
No alternatives available	97	64	0.40	0.94	[0.75 – 1.19]
Alternatives available	172	125	0.42		
ATMPs	7	3	0.30	0.72	[0.28 – 1.87]
Non-ATMPs	262	186	0.42		
Targeted	244	167	0.41	0.87	[0.63 – 1.20]
Non-targeted	25	22	0.47		

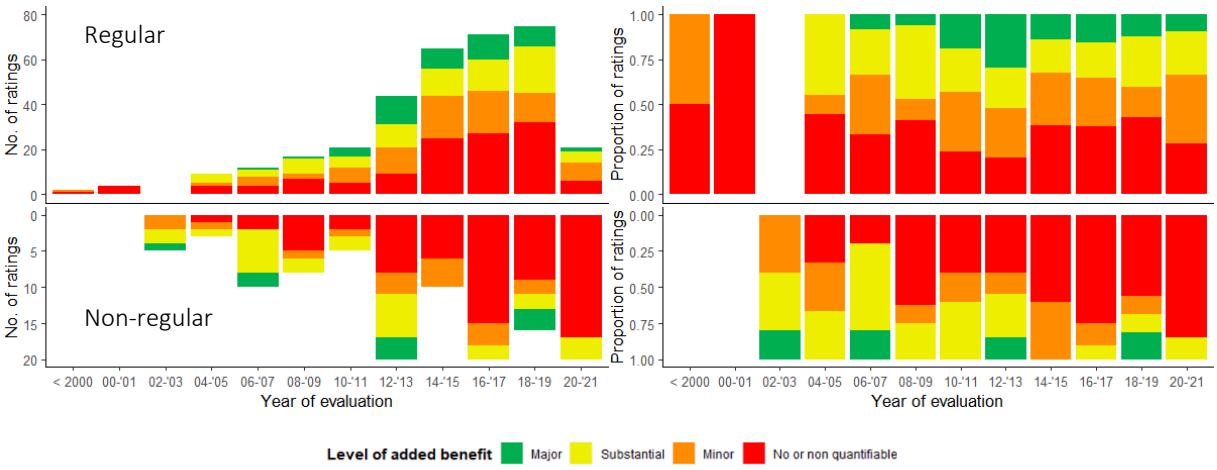


Figure 5: Absolute (left) and proportional (right) bar chart of the distribution of regular approvals (above) and non-regular approvals (below) among the four levels of AB over time. Year of evaluation refers to the year of AB evaluation.

3.2.2 Ratings of HTA agencies and Prescrire over time

Next, the ratings of the HTA agencies (HAS, G-BA, ICER, and AIFA) were analyzed together with those of Prescrire (n = 366). Figures 6 – 7 provide an overview of the acquired ratings over time. The reduction in major benefit ratings between 2010 and 2016 as compared to Figure 4 is due to the exclusion of ESMO-MCBS and ASCO-NHB ratings. The scarcity of ratings of major benefit can also be seen in Figures 6 – 7; in six of the 12 temporal categories, none of the ratings are classified as major benefit. Overall, 189 ratings (52%) in this study cohort were classified as no/non-quantifiable benefit.

From Figure 7, it is clear that the amount of ratings of each of the levels of AB increases over time. From 2012 to 2019, the number of no/non-quantifiable benefit ratings increases considerably. However, the same period in the proportional bar chart shows that the distribution amongst the four levels of AB stays relatively the same over time. In the first half of the study period (1997 – 2010), 33

ratings (48%) were classified as no/non-quantifiable AB, compared to 156 ratings (53%) in the period between 2011 and 2021. With regard to the last few years (2016 – 2021), 106 ratings (55%) were classified as no/non-quantifiable AB.

Next, a subgroup analysis was performed on the AB ratings of the HTA agencies and Prescrire. In Annex VII, the distribution of the subgroups among the levels of AB is shown with regard to the HTA agencies and Prescrire. Again, a significant association was only found between approval type and AB, with an RR of 1.41 (95% CI 1.17 – 1.71, p < .001), meaning that non-regular approvals were rated as having no AB 1.4-fold more compared to regular approvals (Table S4, Annex VII). Regarding the remaining subgroups, no significant associations were found between the characteristics of the subgroups and the level of AB. We also did not find a clear time trend in any of the subgroups, which is elaborately discussed in Annex VII.

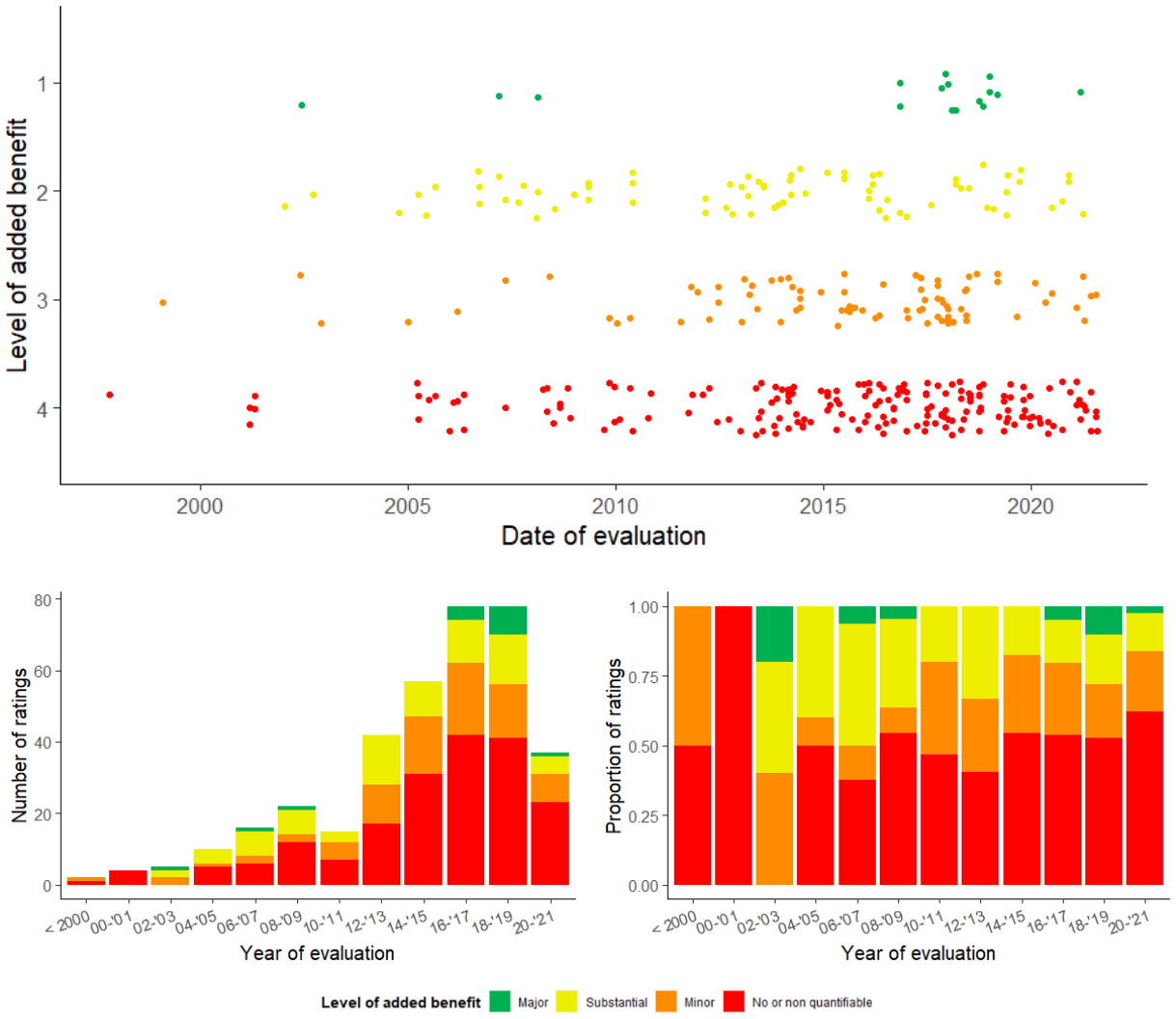


Figure 6 – 7: Above: scatterplot with all AB ratings of the HTA agencies and Prescrire (*n* = 366) over time. Below: absolute (left) and relative (right) numbers of AB ratings of the HTA agencies and Prescrire (*n* = 366) over time. Date/year of evaluation refers to AB evaluation.

3.2.3 ESMO-MCBS and ASCO-NHB scores over time

Subsequently, the ESMO-MCBS and ASCO-NHB scores (*n* = 92) were analyzed over time. The first evaluations of both frameworks date from 2004, hence, in the following figures the years prior to 2004 are left out. Figures 8 – 9 show an overview of the acquired ratings over time and their distribution among the, in this case, three levels of AB. Overall, 20 ratings (22%) were classified as the lowest level of AB, which is minor AB. No ratings of this level of AB have been allocated after 2017. Furthermore, Figure 9 shows that the proportion of major benefit ratings has been decreasing since 2012 – 2013. The number of substantial AB ratings shows the exact opposite trend, and proportionally increases since 2012 – 2013. In the first half of the study period (2004 – 2012), 33% of the ratings were classified as minor benefit, compared to 17% in the second half of the study period (2013 – 2021).

While assessing the individual subgroups in the ESMO and ASCO cohort, we found no statistically significant associations between AB and any subgroup, except in the targeted treatments subgroup (Table S5, Annex VIII). However, as the non-targeted group only contained five indications (one in the high AB group and four in the low AB group), no robust conclusions could be drawn. Furthermore, no robust time trends were found (see Annex VIII).

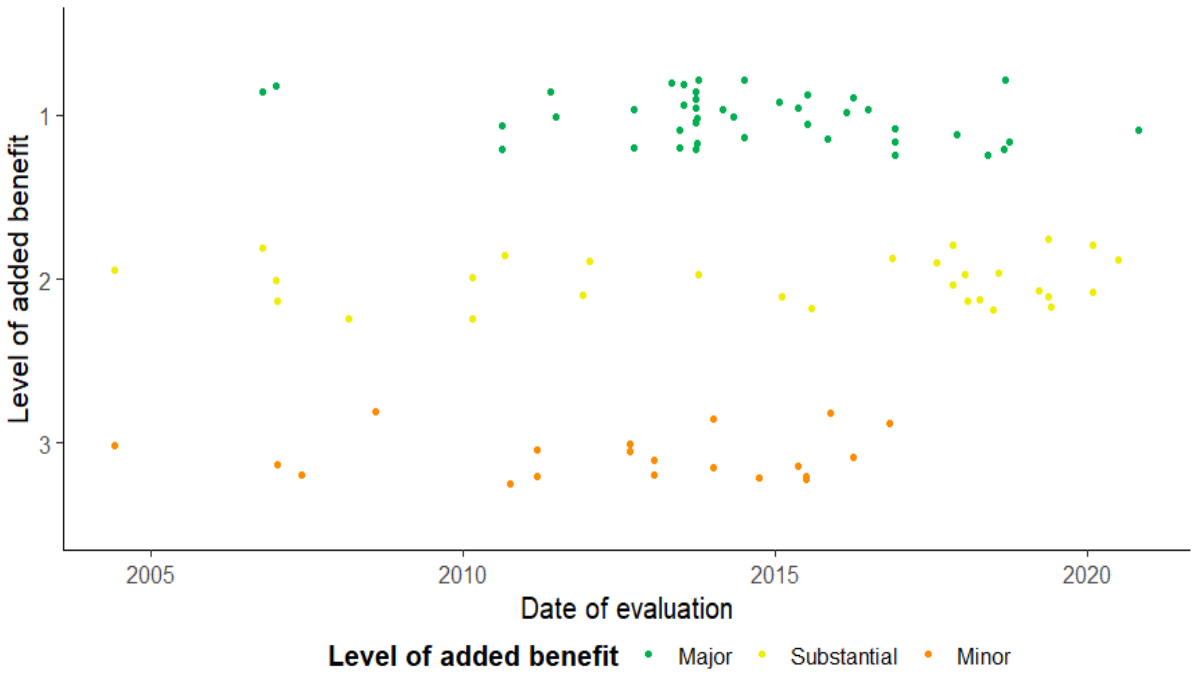


Figure 8: Scatterplot with all AB ratings of ESMO and ASCO over time (*n* = 92). Date of evaluation refers to AB evaluation.

Figure 9: Absolute (left) and relative (right) numbers of AB ratings of ESMO and ASCO (*n* = 92) over time. Year of evaluation refers to AB evaluation.

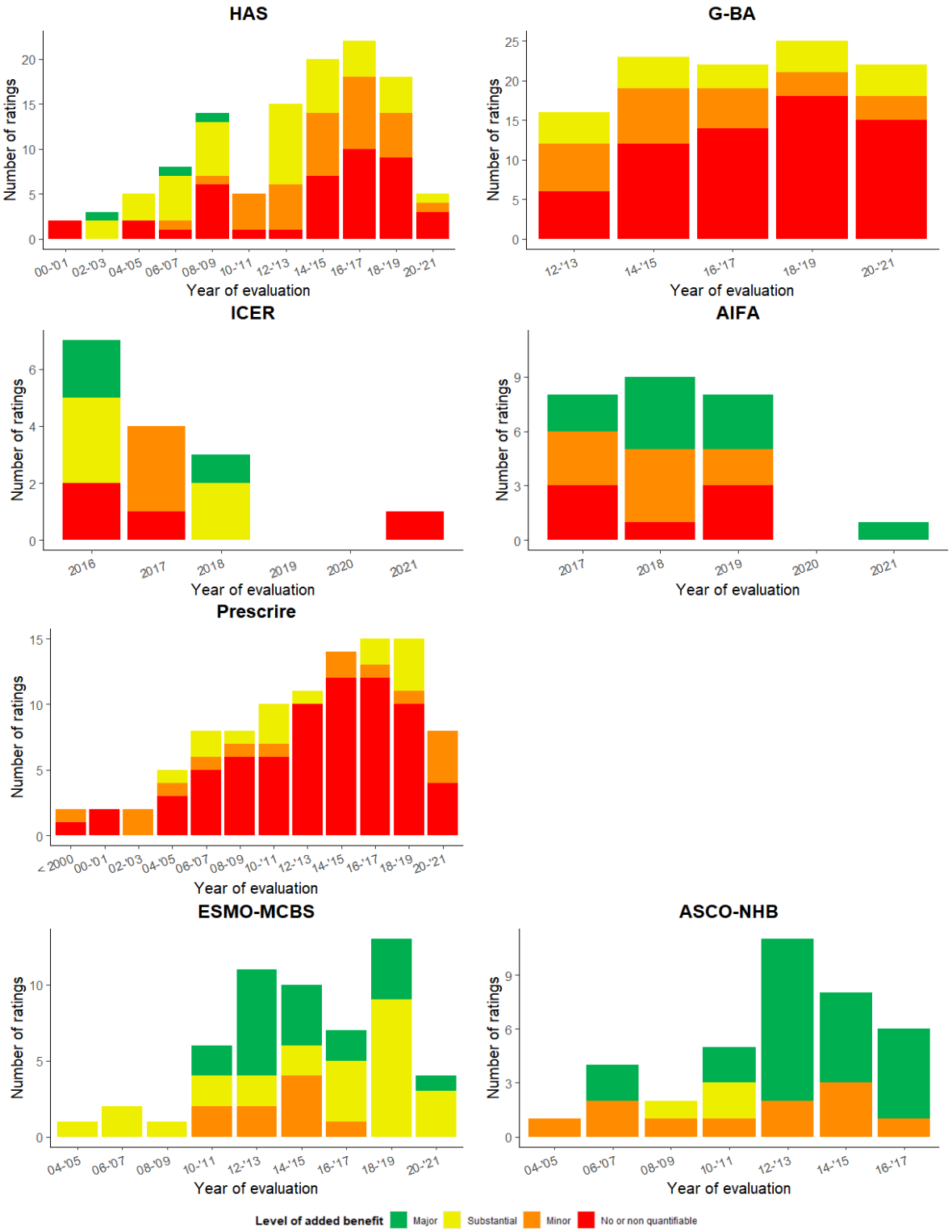
3.2.3 Ratings of individual agencies over time

As a final analysis regarding AB, all included agencies were analyzed individually over time. Figure 2 shows the overall acquired ratings per agency. In Figures 10 – 16, bar charts are shown that display the ratings of each agency over time. Furthermore, corresponding proportional bar charts are enclosed in Annex IX.

There are considerable differences between the distributions among the levels of AB of the agencies. Ratings of Prescrire and G-BA, for example, are and have always been predominantly negative. With regard to HAS, we see that positive AB ratings were assigned much more frequently in the first half of the study period (2000 – 2009) in comparison to the second half. Next, ratings of AIFA and ICER do not show a clear time trend. The small sample sizes (*n* = 26 and *n* = 15, respectively) and narrow time frame also do not allow us to draw firm conclusions. Figure 13 shows no ratings being allocated in 2020, as these were all excluded due to being assigned more than 1.5 years after EMA approval. Of all agencies, ASCO has the highest proportion of major benefit ratings, namely 23 out of 37 ratings (62%). Next, ratings of ESMO are predominantly classified as either major or substantial benefit. However, both frameworks only have three, purely positive, levels of AB.

Last, for each individual agency, subgroups were investigated (Table S6, Annex IX). For two of the agencies (G-BA and ICER) we found a significant association between the level of AB and approval type, in which non-regular approvals were more likely to be rated as having no AB. As this finding was consistently seen amongst the agencies, as well as in the main analysis, we consider this a robust result. Furthermore, we also found significant associations between ratings of Prescrire and G-BA with solid/haematological malignancies, ESMO with targeted/non-targeted therapies, and G-BA with

ATMP/non-ATMPs. However, we do not consider the latter two associations to be meaningful, as there were only three non-targeted and three ATMPs included in the respective analyses. Furthermore, the direction of the association of the solid/haematological subgroup of Prescrire was contrary to the one of G-BA. Thus, as we did not consistently see a robust association in the main analysis or among the individual agencies, we do not consider these associations to be strong or meaningful.

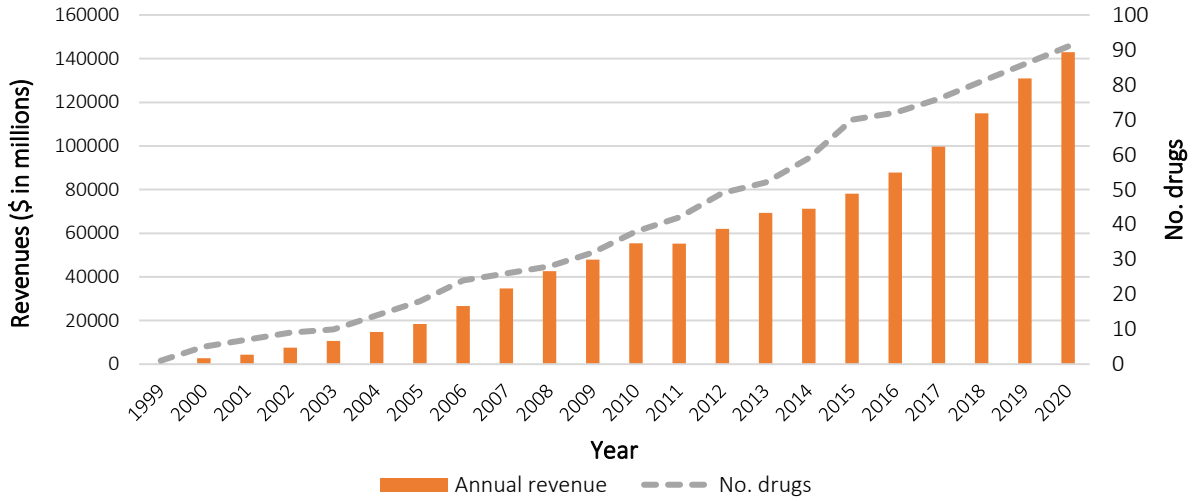


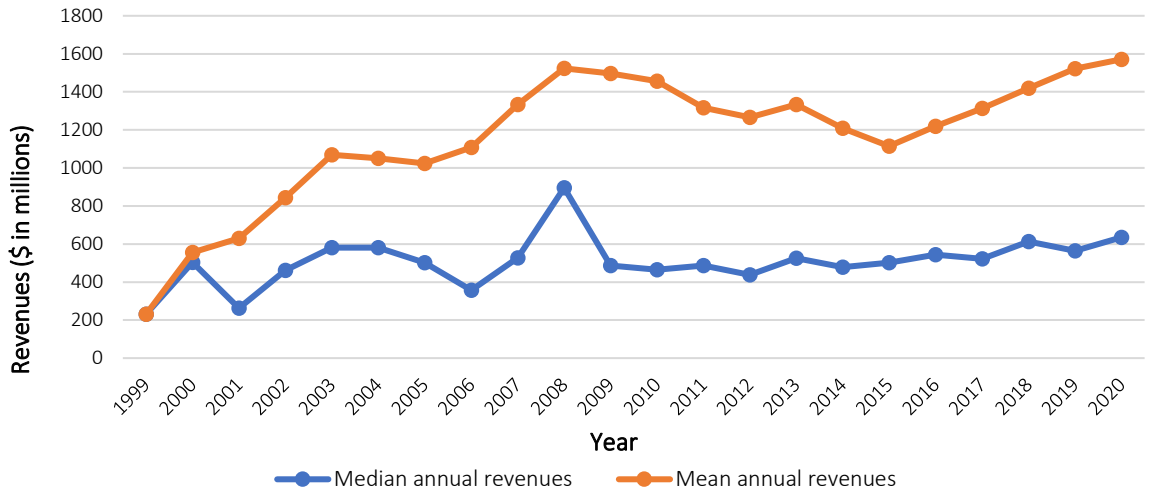
Figures 10 – 16: Acquired ratings of HAS (*n* = 117), G-BA (*n* = 108), ICER (*n* = 15), AIFA (*n* = 26), Prescrire (*n* = 100), ESMO (*n* = 55) and ASCO (*n* = 37) over time. Year of evaluation refers to AB evaluation.

3.3 Revenues

3.3.1 General trend oncology field

Figure 17 shows annual revenues of all included oncology drugs summed up. Annual revenue in the oncology field of approved drugs increased from $231 million in 1999 (*n* = 1) to $142,979 million in 2020 (*n* = 109). As is evident from the figure, the number of drugs of which revenue data is available increases steadily each year (in line with increased approvals). Furthermore, Figure 18 shows the mean and median annual revenues. Their discrepancy indicates skewed data due to some drugs generating disproportionate revenues. Whereas the mean annual revenues increased 6.8-fold (from $231 to $1571 million), the median annual revenues increased 2.7-fold (from $231 to $635 million) between 1999 and 2020. The median annual revenues fluctuate around $500 million since 2000.





Year	'99	'00	'01	'02	'03	'04	'05	'06	'07	'08	'09	'10	'11	'12	'13	'14	'15	'16	'17	'18	'19	'20
No. drugs	1	5	7	9	10	14	18	24	26	28	32	38	42	49	52	59	70	72	76	81	86	91

Figures 17 – 18: Above: cumulative annual revenues of the oncology field (*n* = 109) between 1999 and 2020. Below: mean and median annual revenues per product between 1999 and 2020. The table shows the number of drugs per year.

3.3.2 Cumulative revenues from moment of market entry

Figure 19 shows cumulative revenue data of all products, including the median and IQR per year. There are a few drugs in the dataset that have generated disproportionate amounts of revenues, with three drugs generating cumulative revenues above $100 billion (MabThera, $107 billion, approved in 1998; Herceptin, $104 billion, approved in 2000; Avastin, $102 billion, approved in 2005). However, note that MabThera also has several indications outside oncology. The decline in cumulative revenues in year 18 – 19 is most likely caused by the omission of Avastin, which has been on the market for 17 years and generated the highest revenues in almost all preceding years.

Year	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
No. drugs	109	103	94	88	81	76	64	55	51	43	37	31	27	25	23	17	14	10	9	7

Figure 19: All acquired cumulative revenues/sales data plotted in one figure. The black dots indicate the median of each year, and the bars indicate the IQR.

Next, we concentrated on the first eight years of generating revenues (see Figure 20). Median cumulative revenues were compared to estimates of R&D costs of a single cancer drug (median R&D costs $794 million, range $219 million – $2827 million) (11). Table 3 shows the number of drugs per year and the proportion that has generated more than median and maximum R&D costs. After three years from the moment of market entry, the median cumulative revenue of the study cohort intersects the median R&D costs, meaning that approximately 50% of the drugs in the cohort had a positive ROI (45% after correcting for missing minor products), whereas three years later, already 82% of the drugs (76% after correction) had a positive ROI. Furthermore, seven years after the moment of market entry, 53% of the included drugs (49% after correction) had generated more revenues than the maximum R&D costs of $2827 million. Last, six years from the moment of market entry, 95% of the drugs (85%

after correction) had a positive ROI, and 70% (63% after correcting) had generated more than the maximum estimated R&D costs.

Moreover, Mann-Whitney U tests were performed to assess the differences in the median cumulative revenues at year 5 between the subgroups (see Annex X). A statistically significant difference was only found between curative and non-curative treatments, with curative treatments generating $519.9 million and non-curative $2068.6 million at year 5 ($p = 0.031$), see also Figure 21. Table 4 shows that 67% (50% after correction) of the curative drugs generated a positive ROI after 10 years ($n = 2$), compared to 98% (87% after correction) of the non-curative drugs ($n = 39$). Numerical differences were also present between regular and non-regular approvals and treatments with and without alternatives (see Table S8), but these were not statistically significant.

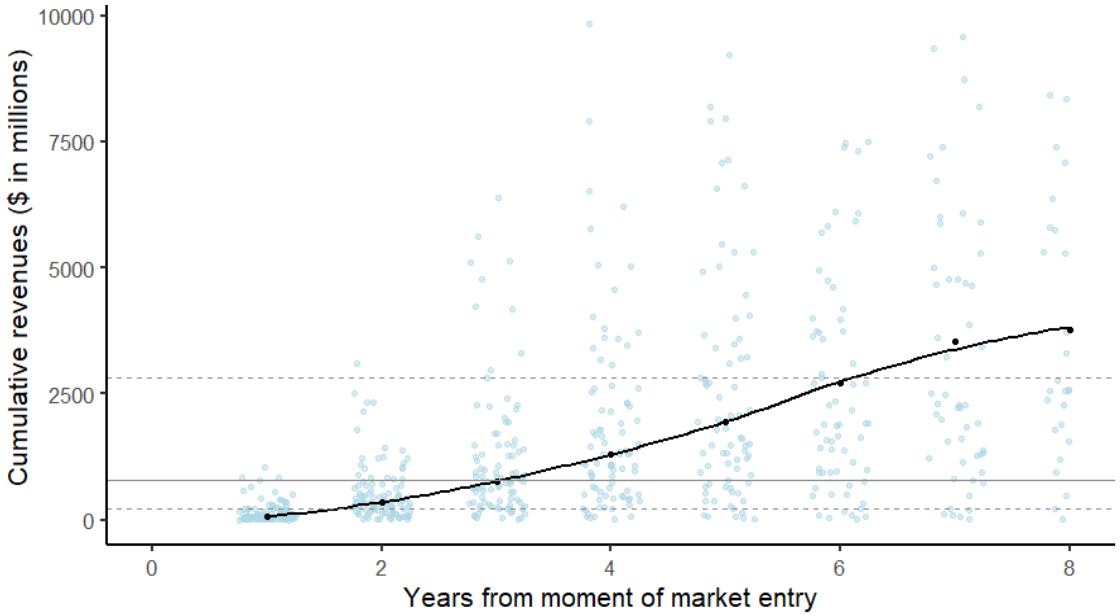


Figure 20: First eight years of generating revenues. The black curve indicates the median in each year, and the gray lines indicate the estimated R&D costs (median of $794 million, range $219 million – $2827 million).

Table 3: The number of drugs per year of which revenue data was available, as well as the number of drugs that generated more than the median and maximum R&D costs.

Year	1	2	3	4	5	6	7	8	9	10
No. drugs with revenue data available	109	103	94	88	81	76	64	55	51	43
Minor products missing	14	13	9	8	7	6	6	6	6	5
Total	123	116	103	96	88	82	70	61	57	48
No. > $794 million (%)										
Not corrected	3 (3)	22 (21)	46 (49)	60 (68)	61 (75)	62 (82)	55 (86)	50 (91)	47 (92)	41 (95)
Corrected	3 (2)	22 (19)	46 (45)	60 (63)	61 (69)	62 (76)	55 (79)	50 (82)	47 (82)	41 (85)
No. > $2827 million (%)										
Not corrected	0 (0)	1 (1)	9 (10)	20 (22)	29 (36)	35 (46)	34 (53)	31 (56)	33 (65)	30 (70)
Corrected	0 (0)	1 (1)	9 (9)	20 (21)	29 (33)	35 (43)	34 (49)	31 (51)	33 (58)	30 (63)

Figure 21: Cumulative revenues of curative and non-curative drugs. The grey lines indicate estimates of R&D costs (median of $794 million, range $219 million – $2827 million).

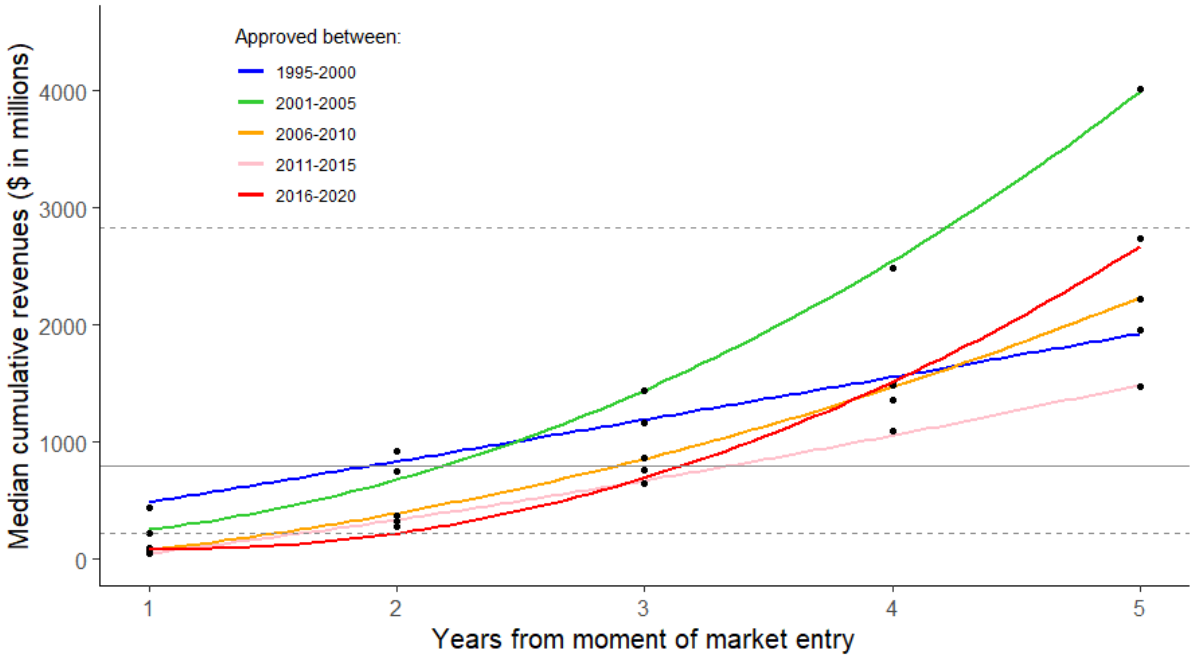
Table 4: The number of curative and non-curative drugs per year of which revenue data was available, as well as the number of drugs that generated more than the median and maximum R&D costs.

Year	1	2	3	4	5	6	7	8	9	10
No. drugs with revenue data available										
Curative	9	7	7	7	6	6	5	4	4	3
Non-curative	100	96	87	81	75	70	59	51	47	40
Minor missing products										
Curative	2	2	2	2	2	2	2	2	2	1
Non-curative	12	11	7	6	5	4	4	4	4	4
Total										
Curative	11	9	9	9	8	8	7	6	6	4
Non-curative	112	107	94	87	80	74	63	55	51	44
No. > $794 million (%)										
Curative	1 (11)	1 (14)	1 (14)	2 (29)	1 (17)	3 (50)	3 (60)	3 (75)	3 (75)	2 (67)
Non-curative	2 (2)	21 (22)	45 (52)	58 (72)	60 (80)	59 (84)	52 (88)	47 (92)	44 (94)	39 (98)
No. > $2827 million (%)										
Curative	0 (0)	0 (0)	1 (14)	1 (14)	1 (17)	1 (17)	1 (20)	1 (25)	1 (25)	2 (67)
Non-curative	0 (0)	1 (1)	8 (9)	19 (23)	28 (37)	34 (49)	33 (56)	30 (59)	32 (68)	28 (70)
No. > $794 million (%)*										
Curative	1 (9)	1 (11)	1 (11)	2 (22)	1 (13)	3 (38)	3 (43)	3 (50)	3 (50)	2 (50)
Non-curative	2 (2)	21 (20)	45 (48)	58 (67)	60 (75)	59 (80)	52 (83)	47 (85)	44 (86)	39 (87)
No. > $2827 million (%)*										
Curative	0 (0)	0 (0)	1 (11)	1 (11)	1 (13)	1 (13)	1 (14)	1 (17)	1 (17)	2 (50)
Non-curative	0 (0)	1 (1)	8 (9)	19 (22)	28 (35)	34 (46)	33 (52)	30 (55)	32 (63)	28 (64)

* corrected for missing minor products

3.3.3 Cumulative revenues for different approval periods

The last revenue analysis focused on the first five years of generating revenues for different approval periods. Figure 22 shows the median cumulative revenues per year from market entry for five time intervals. The curves have relatively similar courses and do not differ considerably. Thus, the differences between the temporal categories are most likely caused by inter-drug variability, rather than the effect of time.



Category	Year 1	Year 2	Year 3	Year 4	Year 5
1995-2000	8	8	8	8	8
2001-2005	10	10	10	10	10
2006-2010	16	16	16	16	16
2011-2015	35	35	35	35	35
2016-2020	40	34	25	19	12

Figure 22: First five years of generating revenues from the moment of market entry regarding different approval periods. The number of drugs per year is shown for each category.

3.4 Association added benefit and revenues

Linear regression analysis was performed to assess if AB is associated with cumulative drug revenues three years from the moment of market entry. We did not find a significant association with regard to the whole study cohort (Table 5) nor for the majority of the individual agencies (Table S9, Annex XI). Only in the case of ESMO, the incremental step from minor AB to major AB resulted in a significant increase in cumulative revenues of $1440 million (95% CI $233 million – $2647 million). Figure 23 and Table 3 show that there are numerical differences in drug revenues at year three between the levels of AB, in which cumulative revenues are higher for indications with more AB, however, these findings are not statistically significant.

Last, a sensitivity analysis was performed, in which only the drugs were included that had one single indication at the end of follow-up (*n* = 45). A statistically significant association was found for the incremental step from no/non-quantifiable AB to substantial AB, and from no/non-quantifiable AB to major AB, which resulted in an increase in cumulative revenues of $506 million (95% CI $125 million – $886 million) and $502 million (95% CI $89 million – $915 million), respectively (see Table 6 and Figure 24). Thus, the sensitivity analysis validates the numerical differences that were found during the main analysis. Furthermore, Table S10 (Annex XI) shows the association between AB and cumulative revenues at year 3 for the individual agencies. A significant association was only found for Prescrire, in which the incremental step from no AB to substantial AB resulted in an increase in cumulative revenues of $1827 million (95% CI $1027 – $2628).

Table 5: Results of the linear regression of all drugs from which revenue data in year 3 was available and at least one AB rating (*n* = 70).

	Revenues (increment, $ in millions)	95% CI ($ in millions)	Significance level
Intercept (no/non-quantifiable AB) (*n* = 136)	1445	[1175 – 1714]	Ref.
Minor AB (*n* = 85)	– 67	[-501 – 367]	0.761
Substantial AB (*n* = 101)	+ 220	[-192 – 633]	0.294
Major AB (*n* = 61)	+ 454	[-29 – 938]	0.066

Table 6: Results of the linear regression of the sensitivity analysis, in which only products were considered that had one indication at the end of follow-up (*n* = 45). Statistically significant results are indicated in bold.

	Revenues (increment, $ in millions)	95% CI ($ in millions)	Significance level
Intercept (no/non-quantifiable AB) (*n* = 50)	740	[490 – 990]	Ref.
Minor AB (*n* = 32)	- 161	[-562 – 239]	0.4275
Substantial AB (*n* = 38)	+ 506	**[125 – 886]**	**0.0065**
Major AB (*n* = 29)	+ 502	**[89 – 915]**	**0.0175**

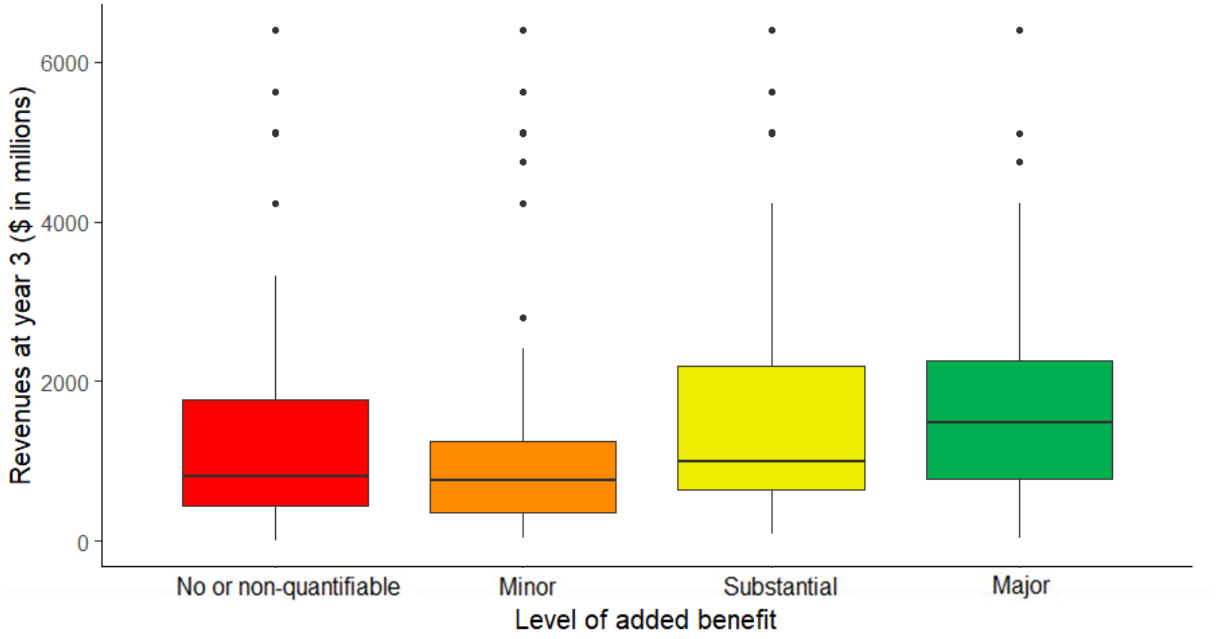


Figure 23: Boxplot that shows the relation between cumulative revenues at year 3 and AB.

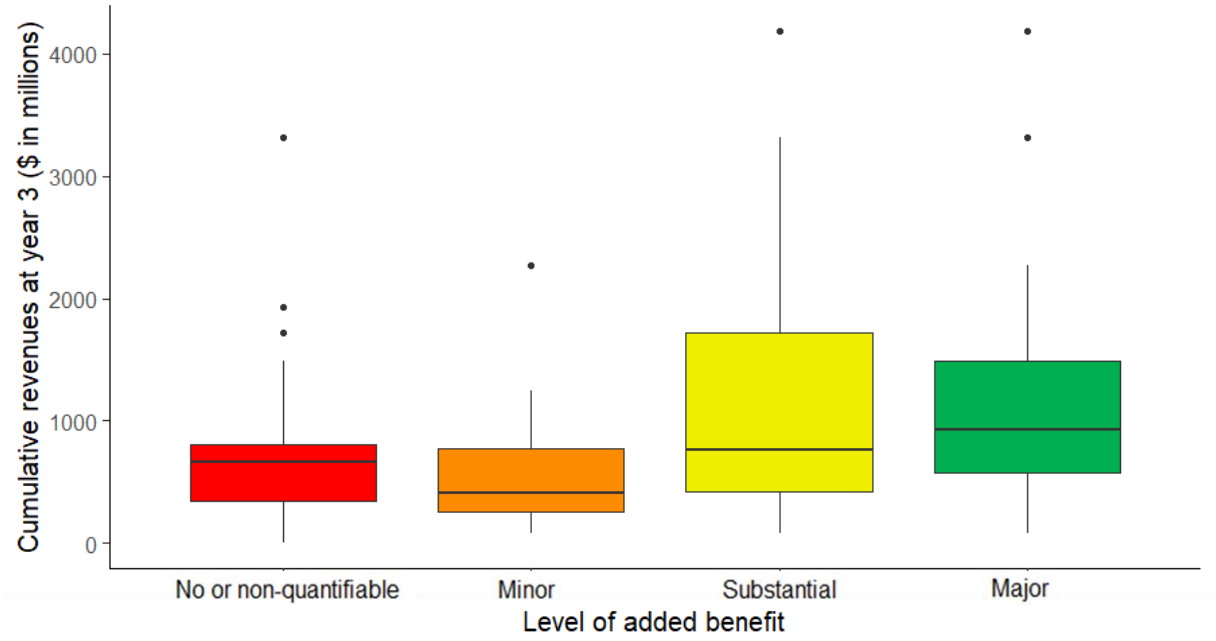


Figure 24: Boxplot that shows the relation between cumulative revenues at year 3 and AB regarding the cohort of the sensitivity analysis.

4. Discussion

4.1 Summary of the findings

AB ratings were mainly classified as having no/non-quantifiable AB throughout all years since 1995. A robust time trend in AB ratings was not found regarding the whole study cohort nor on the subgroup level. The extent of demonstrated AB of oncology drugs has been and remains considerably poor. Only AB and approval type were significantly and meaningfully associated, indicating that non-regular approvals were even more often rated as having no AB. Similar to the AB ratings, median annual revenues per drug have stayed relatively constant over time, indicating that revenues have stayed constant through higher prices for smaller patient populations. Furthermore, we found curative drugs to generate significantly less revenues than non-curative drugs, implying that it has been relatively more challenging to develop and market a successful curative cancer drug. Last, AB and drug revenues were found not to be associated, although numerical differences indicated drugs with higher AB to generate higher revenues. This was validated by a sensitivity analysis that only included drugs with one indication at the end of follow-up, in which a statistically significant association was found.

4.1.1 Added benefit

Overall, 41% of all acquired AB ratings were negative, with HTA organizations and Prescrire providing even larger proportions of negative ratings (52%), whereas the included clinical frameworks provide no negative ratings owing to the positive character of those rating mechanisms. The finding that (HTA) AB ratings are often negative is in line with previous studies (8,33–36).

We found approval type to be significantly associated with AB ratings. Non-regular approvals include conditionally authorized drugs and drugs approved under exceptional circumstances, that are intended for patients with high unmet medical needs and it may therefore be expected that addressing those needs would result in higher AB ratings. However, our results indicate that this potential to address unmet medical needs may be negated by the lack of comprehensive evidence inherent to these approval types, resulting in predominantly negative AB ratings. A study by Vivot et al. likewise explored the association between AB and drug characteristics, including innovation level, orphan status, fast-track, priority review, breakthrough designation and accelerated approval (8). No significant association with any of the characteristics was found. We did find a significant association for approval type, which may be explained by the difference between CMA and AEC and the FDA approval types included in their study. Similarly, other studies found high numbers of negative AB ratings for expedited drugs (33,37–40). All these findings imply that drugs approved through expedited pathways, which are meant to facilitate access to promising drugs, do not necessarily demonstrate an AB at the time of initial evaluation.

For the remaining subgroups, no significant associations were found. This implies that in those cases, the characteristic of the subgroup (e.g. curative intent) was not decisive in the AB evaluation. Apparently, even when investigating all oncology drugs that have ever been approved through the EMA, no subgroup of drugs has a higher potential to demonstrate an AB over others, except for the non-regular approval group as opposed to the regular approved group. Our results emphasize the findings from previous studies that many factors play a role in the evaluation of AB, and that no single factor is decisive (6,39,41).

We did not see a robust time trend in the acquired AB ratings. The ratings of the HTA agencies and Prescrire were found to be quite evenly distributed among the four levels of AB over time, and ratings of the ESMO-MCBS and ASCO-NHB fluctuated but also showed no robust trend. The same picture was seen in the subgroup analyses, where we only found a weak time trend in the approval type subgroup. Thus, AB ratings were found not to be associated with time. This finding is confirmed by several studies. First of all, a study by Saluja et al. found ESMO-MCBS and ASCO-NHB scores that were allocated between 2006 and 2015 not to be associated with time, a similar result to a study of Becker et al (9,42). In both studies, the authors utilized the frameworks to assign the AB scores themselves, whereas we chose to adopt scores that had been allocated by the developers of the frameworks. As a result, indications of our cohort that had not been scored by the developers were treated as missing data, whereas Becker et al. and Sajula et al. were able to score all drugs in their cohort. However, our cohort of ESMO-MCBS and ASCO-NHB ratings was still similar (*n* = 92) to those of the authors in question (*n* = 84 and *n* = 110, respectively). Furthermore, Howard et al. found new cancer drugs not to be significantly associated with greater survival benefits, a measure that is used as an objective scale for quantifying AB, in comparison to older therapies in the period between 1995 and 2013 (43), a similar result to a study by Davis et al. (34). In comparison to these studies, our study is unique in assessing a large cohort of indications during a wide time-frame. In addition, we included AB ratings of seven independent agencies, whereas other studies often limit their inclusion to one or two agencies.

4.1.2 Revenues

We found median revenues per product to fluctuate around $500 million per year irrespective of the moment of approval. This finding implies that annual earnings per product, when corrected for inflation, have not necessarily been rising since 2000. Similarly, the rates of generating revenues in the first years after approval in different approval periods were found to be relatively similar, indicating that also the rate of generating revenues of oncology drugs has not changed over time. The differences that were found were mainly caused by inter-drug variability rather than any effect of time.

In contrast to revenues, drug prices have been shown to increase over time, which is a finding that has been confirmed by many studies (7,9,17,43). Combined with our findings, this implies that less products are sold for a higher price, resulting in similar revenues over time. This could possibly be explained through the fact that more drugs are being developed for small patient groups, due to the introduction of incentives such as the Orphan Drug Act (ODA) in the USA and the Orphan Drug Regulation in the EU that encourage pharmaceutical companies to develop drugs for rare diseases (44–46). Our results also indicated revenues for orphan drugs to be similar to those of non-orphan drugs, which implies that more expensive orphan drugs, intended for small patient populations, result in similar revenues. More research is necessary to address this topic in more detail.

When looking at absolute spending on oncology drugs, a recent paper by Meyers et al. studied the trend in drug revenues among major pharmaceuticals between 2010 and 2019 (47). To our knowledge, Meyers et al. are one of the first that specifically focused on drug revenues as a measure of earnings, instead of drug prices. They found total revenues in the oncology field to equal $55.8 billion and $95.1 billion in 2010 and 2019, respectively, an increase of 70%. Based on our own data, we found total drug revenues to increase from $55.4 billion in 2010 to $130.9 billion in 2019, which is an increase of 136%. Drug revenues of both studies are very similar in 2010, whereas our obtained drug revenues in 2019 are 1.4 fold higher. Meyers et al. limited their study cohort to drugs of ten major pharmaceutical companies, whereas we included all oncology drugs approved by the EMA between 1995 and 2020. We expect that our dataset includes considerably more drugs that are marketed by smaller pharmaceutical companies at the end of the study period, resulting in the significant difference in total drug revenues in 2019. Our findings emphasize the conclusion in the previous study that revenues of the oncology field have been increasing over time. Meyers et al. correctly pointed out that further research is needed to investigate how this increase in revenues reflects industry profits.

After analyzing cumulative revenues per product, we found the median cumulative revenues to intersect with the estimated median R&D costs after three to four after the moment of market entry, and after six to seven years with the maximum R&D costs. Furthermore, six years from the moment of market entry, 82% of the drugs (76% after correction) had generated a positive ROI. We chose a conservative approach in which we assumed the missing minor products not to have generated more than estimated R&D costs in any of the years. High prices of oncology drugs are often justified by the need to finance R&D costs, however, our findings imply that the majority of cancer drugs achieve a positive ROI within a few years from market entry. The conclusions were similar on a subgroup level, with the exception of curative treatments that were found to have generated significantly less revenues at year 5 in comparison to non-curative treatments. After six years (eight

years after correction), at least half of the curative drugs achieved a positive ROI, whereas this was after three years (four years after correction) for non-curative drugs. This finding suggests that it is more challenging to develop and market a successful curative cancer drug. Other reasons for significantly lower revenues of curative drugs could possibly be a shorter treatment duration. However, due to the small sample size of the curative group at year 5 (*n* = 8), we cannot draw firm conclusions. Future research could repeat this analysis with a larger sample size of curative drugs.

Drug revenues have previously been compared to corresponding R&D costs. A study by Prasad et al. found that total R&D spending of a study cohort with ten cancer drugs equalled $9 billion, whereas total revenue after a median time of four years turned out to be 7-fold higher, namely $67 billion (11). Since we do not have specific R&D costs of each drug that we included in our cohort, we cannot make such a comparison. We found total cumulative revenues four years after market approval to be $186,367 million (*n* = 89). If we assume each drug to have R&D costs that equal the estimated median R&D costs of $794, this would result in total R&D costs of $70,666 million; thus, total revenues are 2.6-fold higher than the estimated R&D costs. This is relatively in concordance with the findings by Prasad et al.

4.1.3 Association added benefit and revenues

The analysis of the association between AB ratings and cumulative revenues three years from the moment of market entry for each of the agencies showed that overall no clear relation was found between AB and drug revenues. A statistically significant result was not found for any of the agencies, except for ESMO, in which the incremental step from minor AB to major AB resulted in a significant increase in revenues of $1440 million (95% CI $233 million – $2647 million). For the other agencies, we did observe numerical differences, with drug revenues increasing for higher levels of AB. This was found in the overall analysis, as well as for HAS and ICER (see Annex XI). However, for these agencies, the number of major AB occurrences was low in the regression analyses, with *n* = 5 for HAS and *n* = 3 for ICER. However, the sensitivity analysis did yield statistically significant results, which validates our findings. We expected drug revenues to be in line with AB, i.e. drugs with higher AB generate higher revenues. Even though we only found statistical evidence to support this during the sensitivity analysis, we did find numerical results that indicate drugs with higher AB to generate higher revenues for some agencies. Previous studies have already focused on the relation between AB and drug prices, in which no significant associations were found (7–9,14,16,17). Our study is, at the time of writing, the first to explore the association between AB and drug revenues. Future research could extend this analysis by adding more variables to the regression model, such as year of approval, therapeutic area, and approval type.

4.2 Strengths and limitations

This study distinguishes itself from previous research, as it is the first to relate AB to drug revenues. We believe drug revenues to be a more accurate measure of what is earned with a drug, as drug prices are often prone to confidential price negotiations and very dependent on a country's willingness or ability to pay. Another strength of this study is that it encompasses a large period of time and a complete cohort, as we focused on all oncology drugs approved by the EMA between 1995 and 2020. Last, AB ratings were obtained from seven different evaluation agencies (four HTA organizations, Prescrire, ESMO and ASCO).

This study has limitations. First, not all agencies evaluated the AB of each indication. Especially regarding drugs that have been approved around the year 2000, there is a lot of data missing. Second, it occurred that only revenues of the major (i.e. more successful) products were reported in financial reports of pharmaceutical companies (n = 14). Thus, we assume these products to be minor (less successful than the other drugs), resulting in our estimate of the median revenues to be higher than the true median. However, we did correct for this during the analysis that related AB to drug revenues.

Furthermore, defining AB of a drug or indication is challenging. The reported AB evaluations refer to a benefit that is averaged over all patients that were treated, even though some patients benefit more from a drug with a lower AB rating, compared to a drug with a higher rating (48). Additionally, evaluating agencies all take other aspects into account when assessing a drug, with also the context of the country playing a role (6,39,41). Furthermore, we only focused on the initial indication(s) of novel oncology drugs and evaluated the AB that was based on data submitted for approval, since this reflects the entry into the market. How this benefit evolves over time (including possible new indications) is of interest, but not the focus of this study.

Additionally, some products in our dataset are used for multiple indications, including non-oncolytic indications. Thus, the revenue data that we obtained were attributed to the drugs in an oncolytic setting, whereas this might not be fully the case. However, we did perform a sensitivity analysis in which only products with one indication at the time of follow-up were included. This analysis confirmed the results that were found in the main analysis. Furthermore, we only retrieved data on drug revenues, and are therefore unable to draw conclusion on the profits of the pharmaceutical industry. It is almost impossible to distill profits of companies, given that these are not reported on drug level and confounded by marketing costs. However, a study by Tay-Teo et al. found that pharmaceutical companies earn approximately $15 for every $1 that is spent on R&D (12,49). Further research is needed to explore if industry profits are excessive and in line with the AB of their products.

Moreover, we used an estimate of $794 million to examine returns on R&D investments, even though it can be questioned if one can use the same value for all types of drugs in the cohort. However, we took a conservative approach by also comparing revenues to the maximum estimated R&D costs of $2827 million. Future research could analyze the exact R&D costs of cancer drugs in relation to corresponding revenues, in order to draw more firm conclusions on the return on R&D costs. Furthermore, we considered a drug to have a positive ROI when revenues were higher than the estimated median R&D costs, however, the costs of production and commercialization were not taken into account.

Last, data extraction and categorization was performed by one author and was not independently checked. However, as most of the extracted data (AB ratings, subgroups and revenues) are rather straightforward and do not require subjective interpretation, we do not expect this to have influenced our analysis. However, a sample of the data will be independently checked before future applications of the data.

4.3 Future research

Expressing the AB of novel drugs by means of a rating facilitates prioritization of drugs, as well as justification of corresponding drug prices. During our study, we observed large discrepancies between ratings of a single indication among the included agencies. This is partly explained due to evaluating methods of different agencies being context-dependent, resulting in varying aspects to be taken into account during the evaluations. Still, countries as Germany and France have a relatively similar evaluation system, which might imply that their ratings are in concordance with one another. However, a study by Boucaud-Maitre et al. showed agreement between AB ratings of HAS and IQWiG to be low (50.3%), specifically for antineoplastic agents (50). Comparing ratings between agencies was not the focus of this study, but we advocate that future research focuses on evaluating concordance between more (HTA) agencies, as well as elucidating the reasons behind the discrepancies.

4.4 Conclusion

In conclusion, our study showed that the AB of oncology drugs approved between 1995 and 2020 remains poor, in particular for drugs that are approved via CMA or AEC. These pathways ought to facilitate access to promising drugs, but may be negated by a lack of comprehensive evidence that complicates demonstrating sufficient AB. We did not find a meaningful association between AB and any of the other drug characteristics. Thus, our results emphasize that manufacturers who aim to develop drugs that truly benefit patients should aim not just to develop a drug with —for example—a

novel mechanism of action, but should also make sure that the drug actually addresses an unmet medical need and that the evidence to back up its effects is strong.

Moreover, we found drug revenues to stay constant over time, while drug prices have been shown to increase, implying that drug development is more focused on smaller patient groups (i.e. orphan drugs). Furthermore, a significant association was found between AB and drug revenues, however, this was only the case for the sensitivity analysis. Transitioning to a value-based pricing system, in which drug prices are determined in proportion to the AB that they have, could possibly improve health care spending, as pharmaceutical companies can no longer charge excessive prices to maximize their profits. Future research could explore if profits by the pharmaceutical industry are excessive and/or in line with the corresponding AB, and evaluate the benefits of a value-based pricing system.

Acknowledgements

In the first place, I would like to thank Dr. Rick Vreman for his excellent guidance and support during the entirety of my research project, especially in these uncertain COVID times. Furthermore, I would like to express gratitude to Prof. Dr. Aukje Mantel-Teeuwisse for giving me the opportunity to do my research project under her skilled supervision. Furthermore, I want to thank Dr. ir. Wim Goettsch for being the second reviewer and Dr. Lourens Bloem for his helpful advice, also during the weekly lunch walks together with Rick, Jasmin and Karla. Further, I would like to thank Daan Marselis, Lucien Hordijk and Karen Zaky for giving me access to their dataset, which made the data collection part a little more manageable. Last, I want to thank the whole division of Pharmacoepidemiology and Clinical Pharmacology for the inspiring DiMi sessions and the welcoming atmosphere that I have always felt.

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