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

Supplementary material

Francine Brinkhuis (5536456)

22-12-2021

Contents

Annex I: Information of included drugs and agencies 2
Annex II: Extraction guide of added benefit scores 4
Annex III: Methodology of subgroup assignment 7
Annex IV: Re-categorization of added benefit scores 9
Annex V: Missing revenue data 10
Annex X: Subgroup analysis whole cohort 11
Annex V: Subgroup analysis HTA agencies and Prescrire 13
Annex VI: Subgroup analysis ESMO and ASCO 17
Annex VII: Analysis individual agencies over time 21
Annex IIX: Subgroup analysis drug revenues 25
Annex IX: Association added benefit and revenues 26
References 30

Annex I: Information of included agencies

Table S1: All agencies of which added benefit (AB) ratings were collected, including their key aims and applied scale for quantifying the level of AB.

Agency	Key aims and scope	Applied scale for AB
HAS	HAS is an HTA organization of France. It assesses the clinical benefit and AB of medicinal products from a medical and economic point of view in comparison to existing treatments. It then provides recommendations on the reimbursement of these medical products (1).	• 1 = major CAV • 2 = considerable CAV • 3 = moderate CAV • 4 = minor CAV • 5 = no or not quantified CAV
G-BA	G-BA is an HTA organization of Germany that works closely together with IQWiG. IQWiG makes the assessment reports and formulates a recommendation on the incremental benefit and costs of a product. The G-BA then uses this recommendation to decide on the reimbursement of that product (2). However, the IQWiG does not evaluate orphan drugs. We therefore chose to use the assessments of the G-BA rather than those of IQWiG.	• Major additional benefit • Considerable additional benefit • Minor additional benefit • Non-quantifiable additional benefit • No additional benefit proven • Less additional benefit
ICER	ICER is an HTA organization of the United States that conducts assessments on a selection of healthcare interventions. They assess the clinical data of a novel drug on relative clinical effectiveness, as well as on incremental costs. The results of this are used to calculate a value-based price benchmark for the drug product; a price range that reflects the value of the drug to the healthcare system and patients (3). Even though ICER is an HTA agency, the USA has no national HTA agency that provides guidance on reimbursement decisions, coverage and pricing (4). This is one of the reasons for the difference in drug pricing between the USA and Europe.	• A = Superior • B = Incremental • C = Comparable • D= Negative • B+= Incremental or better • C+ = Comparable or incremental • C- = Comparable or inferior • C++ = Comparable or better • P/I = Promising but inconclusive • I = Insufficient
AIFA	AIFA is an HTA organization of Italy that assesses the level of innovativeness of new medicinal products in relation to their costs. Furthermore, AIFA promotes the rational use of medicines and financially supports independent research projects (5). Even though AIFA was founded in 2004, they have only been sharing their evaluations publicly since 2017.	• Fully innovative • Potential or conditional innovation • Not innovative
Prescrire	Prescrire is a medical journey that is run by the Association Mieux Prescrire, a non-profit organization that operates independently from the pharmaceutical industry. It evaluates new medicinal products on AB based on a risk-benefit analysis and a comparison of the (dis)advantages to existing therapies. Prescrire does not take the incremental costs of new products into account during their evaluations (6).	• Bravo • A real advance • Offers an advantage • Possibly helpful • Nothing new • Judgement reserved • Not acceptable
ESMO	ESMO-MCBS ratings consist of two components (12):	Non-curative:

	i. A preliminary rating based on the therapeutic benefit of the drug according to primary endpoints of the pivotal clinical trial(s). This outcome is linked to a certain score in a prespecified manner. ii. A modification of the preliminary score based on the toxicity of the drug and the quality of life (QoL). For treatments with non-curative intent, a different scale is used than treatments with curative intent. Note that we included scores of both scales in our study. Drugs with a score of A, B, 4 or 5 are regarded as high-priority drugs and should ideally be accessible in all EU countries.	• 5 = substantial benefit • 4 = substantial benefit • 3 = moderate benefit • 2 = negligible benefit • 1 = negligible benefit Curative: • A = substantial benefit • B = substantial benefit • C = moderate benefit
ASCO	Using the ASCO-VF, a net health benefit (NHB) score can be allocated, which consists of three components (7): i. Magnitude of treatment effect: assessed by overall survival (OS) data. When this is not reported, progression-free survival (PFS) or overall response rate (ORR) is used. ii. Toxicity: this component ranges from -20 to +20, in which negative values correspond to a higher toxicity in comparison to the control group, positive values to reduced toxicity, and a value of 0 to similar toxicity. iii. Bonus points: can be awarded if the treatment is associated with long-term benefits, improvement of cancer-related symptoms, improvement of QoL, or elongation of treatment-free interval. The sum of these three components gives the ASCO-VF score. This score is continuous and can range from -20 to 180.	• ≥45 = substantial benefit • 40-45 = intermediate benefit • ≤ 40 = low benefit

AIFA = Agenzia Italiana del Farmaco; ASCO = American Society of Clinical Oncology; ESMO = European Society for Medical Oncology; G-BA = Gemeinsamer Bundesausschuss; HAS = Haute Autorité de Santé; ICER = Institute for Clinical and Economic Review; IQWiG; Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

Annex II: Extraction guide of AB scores

General remark: For each of the agencies, it was always checked if the indication of the evaluation report fully matched the initial indication as approved by the EMA. When a general indication by the EMA was split in several subtypes in an evaluation report (thus resulting in two or more AB ratings), the entry in the dataset was duplicated and the indications were edited to match the subtypes. It was assumed that the AB rating from other agencies (that did not specify the indication to the same extent) were applicable to all subtypes, and was therefore allocated to both entries. An example is Piqray (alpelisib), from which the initial indication as approved by the EMA is; '*Piqray is indicated in postmenopausal women, and men, with hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative, advanced breast cancer with a PIK3CA mutation in combination with fulvestrant after disease progression following an endocrine based regimen'* (8). First, this indication was treated as a single entry in the dataset. During data collection, we found that the G-BA evaluated Piqray differently for two cases, namely, they assess the drug used in the indication for postmenopausal women separately from the one for men (9). As a result, two different AB ratings were obtained; 'minor additional benefit' and 'no additional benefit proven', for women and men, respectively. Thus, we duplicated the entry of Piqray and specified the indication based on gender. All other AB ratings that we found that did not distinguish between men and women were assumed to apply for both subtypes, and were thus allocated to both.

Contrarily, if the EMA indication was specified to e.g. a certain subtype of the disease, specific line of treatment, or specific patient group, it was a requirement that the indication mentioned in the evaluation reports had the same extent of specification. If not, the AB rating was not retrieved, and was reported as *NA* instead. For example, the EMA approved initial indication of Kymriah (tisagenlecleucel) is; '*Kymriah is indicated for the treatment of paediatric and young adult patients up to 25 years of age with B-cell acute lymphoblastic leukaemia (ALL) that is refractory, in relapse post-transplant or in second or later relapse'* (10). In this case, it was a requirement that the indication mentioned in the evaluation reports was specifically targeted at paediatric and young adults up to 25 years old, as well as the disease being refractory, in relapse post-transplant, or in second or later relapse. If this was not specified, the AB rating was not retrieved. Below, it is specified how the AB ratings for each of the agencies were retrieved.

HAS: The search function of the website of the HAS was used to acquire the webpage of each drug product. This was done either on the level of the brand name or the international nonproprietary name (INN) (similar search results were obtained). Then, the first available evaluation report of a drug product was collected. Multiple indications of a single drug, and therefore multiple evaluations, could all be found in the same report of said product. Preferably, an English version of the report was acquired. In those reports, the final Clinical Added Value (CAV) score could be found in the section '*Benefit of the medicinal product*', or '*Improvement in actual benefit*'. If only a French report was available, the document was searched for '*amélioration du service médical rendu*' (ASMR), after which the CAV score was indicated.

ICER: ICER's assessment reports are made on the level of a disease instead of an individual drug product. For example, all evaluated drugs for non-small cell lung cancer are discussed in a single report. The reports could be found on the '*Assessments'* page, in which the filter function was used to acquire the assessment reports of a certain disease. It was checked which report(s) contained drugs that were included in our dataset, and the first available report was downloaded. If available, the '*Report at a glance*' was collected, in which the desired ratings could be found in the section '*ICER evidence ratings*'. If not, the '*Final evidence report meeting summary'* was retrieved, in which the ratings could be found in the results section.

G-BA: The search function of G-BAs website was used to find the evaluation reports. Either the brand name or INN was used as a keyword. The first available '*Beschlusstext'* of each drug was collected and translated to English with Google Translate. The desired AB score could be found by searching the original German report for '*Zusatznutzens'.*

AIFA: On the website of the AIFA, an Excel file with innovativeness assessment reports by therapeutic indication is available (11). In this file, all drugs that have been evaluated by the AIFA are listed, including a link to the corresponding report. The list was checked and all reports of the drugs that were included in our dataset were extracted. The level of AB could either be found in the Excel file, or in the evaluation report in the section '*Giudizio complessivo sull'innovativita*'. Note that the AIFA has not publicly shared its evaluation reports before 2017. Thus, only evaluations that were carried out between 2017 and 2020 could be included.

Prescrire: To get access to Prescrire's assessment reports, a (paid) account at Prescrire is required. The search function was used to find the reports. Reports could only be found by using the INN of a drug as a keyword. The first available report of the correct indication for each drug was retrieved. The AB score could be found in a colored box in the report.

ASCO-VF and ESMO-MCBS: The first version of the ESMO-MCBS was published in 2015 and revised to version 1.1 in 2017. The ASCO-VF was published in 2015 and revised to version 2 in 2016 (12). The revised versions of the frameworks were used for this study. Scores of the ESMO-MCBS v1.1 have been published via online scorecards on the ESMO website (13). These scorecards were used for extraction of the desired scores. Webpages of all the scorecards were saved. Since the date of evaluation was not always reported, the publication date of the most recent scientific article (that was used as reference for the evaluation), was documented as evaluation date.

With regard to the ASCO-VF, an article by Cherny et al. (2019) was used to acquire the NHB scores of the drugs included in our dataset (12). The scores that are reported in this article were determined by members of the ASCO-VF v2 development team themselves. In the supplementary information of said article, detailed information on the evaluations was present. The publication date of the most recent trial that was included in the rating was documented as evaluation date.

Not all drugs that are included in our dataset were available through the ESMO-MCBS scorecards, or evaluated with the ASCO-VF by Cherny et al. (2019) (12). We chose not to complement the missing scores by e.g. retrieving them from other (scientific) sources or scoring them ourselves, in order to prevent inconsistencies in scoring.

Annex III: Methodology of subgroup assignment

Below, specifications are provided on the assignment of subgroups. Note that all subgroups were assigned based on the time of initial approval.

Approval type: regular versus non-regular approvals. The latter include conditional market authorizations (CMAs) and authorizations under exceptional circumstances (AECs). Retrieved via the initial EPARs. The EMA indicates that expedited programs are meant for drugs that are intended for life-threatening diseases to provide a significant improvement over the standard of care (14), and the goal of such programs is therefore to speed up the development of these promising drugs (15). Therefore, the hypothesis is that drugs approved via non-regular pathways have significantly higher AB compared to regular approvals.

Orphan status: orphan drugs versus non-orphan drugs at the time of initial approval. Retrieved through the initial EPARs. The assignment of an orphan drug designation is based on three criteria (16); first, the drug must be intended for a life-threatening or chronical debilitating condition. Second, this condition must not exceed the prevalence of 5 in 10.000, or alternatively, it must be unlikely that without incentives sufficient return on investment will be generated. Last, no satisfactory treatment options may exist, or if they do, the new product must have significant incremental benefit over available treatments. Due to these strict requirements to obtain orphan status, and the expectation of orphan drugs to tackle a high unmet clinical need, our hypothesis is that orphan drugs have significantly higher AB in comparison to non-orphan drugs.

Innovation level: first-in-class versus later-in-class drugs. Innovation level was assigned by data from annual summaries of novel drugs from the FDA and press releases from the EMA, which were available for the years 2011-2020. For years prior to 2011, a study on first-in-class pharmaceuticals by Lanthier et al. (2013) was used (17). First-in-class drugs rely on a novel and unique pharmacological mechanism, by modifying an unprecedented target or biological pathway (18). First-in-class drugs are often considered as promising new treatment options that represent a high level of innovation (7). We therefore expect these drugs to have higher AB compared to later-in-class drugs.

Therapy intent: curative versus non-curative drugs. The ESMO-MCBS distinguishes between therapies with curative intent (including adjuvant treatments), and therapies with a non-curative intent. A scale from A-C is used for the first group, whereas a scale from 1-5 is used for the latter (7). Thus, all available ESMO-MCBS scores were collected first via the scorecards that are available on the website of the ESMO (13). All drugs that had been given a score from 1-5 were categorized as non-curative, and all drugs that had been assigned a score from A-C were categorized as curative. Since not all drugs in the study cohort had been assigned an MCBS score, the missing data was complemented with information from the initial EPARs, as well as evaluation reports from the HAS, in which the therapy intent was reported under *'Actual benefit'* (English reports) and *'Service médical rendu'* in French reports.

Treatments with curative intent aim at letting the patient survive beyond the disease-free survival plateau, that is, the time after which the risk of treatment failure approaches zero (19). Even though numerous oncology drugs are available, only few provide long-term cure (20). Most curative cancer treatments involve surgery, in which the malignant tissue is completely removed. Our hypothesis is that the few curative oncology drugs that are available, fulfil a great unmet clinical need, and therefore have higher AB than non-curative drugs.

Malignancy type: drugs for solid malignancies versus drugs for haematological malignancies. Again, the ESMO-MCBS scores were useful for the categorization of the malignancy type. The ESMO-MCBS is only applicable to solid malignancies. Therefore, if a drug had been assigned any MCBS score, it was automatically categorized as a treatment for a solid malignancy. The missing data was complemented by checking the initial indications. The malignancy type was then assigned based on the categorization by the Cancer Treatment Centers of America (CTCA); multiple myeloma, leukaemia and lymphomas were considered as haematological malignancies (blood cancers), and all other cancer types were considered solid malignancies (21). We do not have an explicit hypothesis on the AB of these groups, but we decided to take this subgroup into account since distinguishments are often made between solid and haematological malignancies in many studies and evaluation methods, such as the ESMO framework.

Availability of alternatives: drugs with alternative treatments versus drugs without alternative treatments. The EPARs were used to allocate this subgroup. The required information could be found in one of the sections '*Available therapies and unmet clinical need*', '*Discussion on the benefit-risk balance*', or the conclusion of the report, in which background information on the standard of care was mentioned. If the required information could not be found in the EPAR, additional information was retrieved via Google with regard to the indication in and the corresponding available therapies and standard of care. Since treatments without alternative treatments tackle a higher unmet clinical need, we expect this group to have higher AB compared to treatments that do have alternatives.

ATMPs: ATMPs vs non-ATMPs. A list of all approved ATMP therapies was obtained via the website of the EMA (22). ATMPs are regarded as upcoming therapies that are meant to *'[…] offer groundbreaking new opportunities for the treatment of disease and injury'* (23). Hence, we expect ATMPs to have greater AB than non-ATMPs.

Targeted therapy: targeted versus non-targeted drugs. Small molecules and antibody treatments were considered as targeted therapies, whereas cytotoxic drugs (chemotherapy) were categorized as being non-targeted. For all other drugs, additional information from the EPARs was consulted to assign the groups. Additionally, a list of targeted therapies of the NCI was consulted (24). Targeted therapy can identify and attack cancerous cells very precisely without affecting normal cells, limiting side effects. Contrarily, non-targeted therapies are much more invasive, since both cancer cells and normal cells are targeted. As a result, adverse effects are more common for non-targeted therapies. Therefore, we expect targeted therapies to have higher AB compared to non-targeted therapies.

Annex IV: Re-categorization of AB scores

Table S2: Re-classification of all possible AB ratings into a new 4-point ranking scale

Agency	Original scale of AB	New classification	
Prescrire	Bravo	1	Major AB
	A real advance		
	Offers an advantage		
	Possibly helpful		
	Nothing new		
	Judgement reserved		
	Not acceptable		
ICER	A = Superior		
	B = Incremental		
	C = Comparable		
	D= Negative		
	B+= Incremental or better		
	C+ = Comparable or incremental		
	C- = Comparable or inferior		
	C++ = Comparable or better		
	P/I = Promising but inconclusive		
	I = Insufficient	2	Substantial AB
HAS	1 = major CAV		
	2 = considerable CAV		
	3 = moderate CAV		
	4 = minor CAV		
	5 = no or not quantified CAV		
G-BA	Major additional benefit		
	Considerable additional benefit		
	Minor additional benefit		
	Non-quantifiable additional benefit		
	No additional benefit proven	3	Minor AB
	Less additional benefit		
AIFA	Fully innovative		
	Potential or conditional innovation		
	Not innovative		
ESMO-MCBS	*Non-curative:*		
	5 = substantial benefit		
	4 = substantial benefit		
	3 = moderate benefit		
	2 = negligible benefit	4	No/non-quantifiable AB
	1 = negligible benefit		
	Curative:		
	A = substantial benefit		
	B = substantial benefit		
	C = moderate benefit		
ASCO-VF	≥45 = substantial benefit		
	40-45 = intermediate benefit		
	≤ 40 = low benefit		

Annex V: Elaboration on missing revenue data

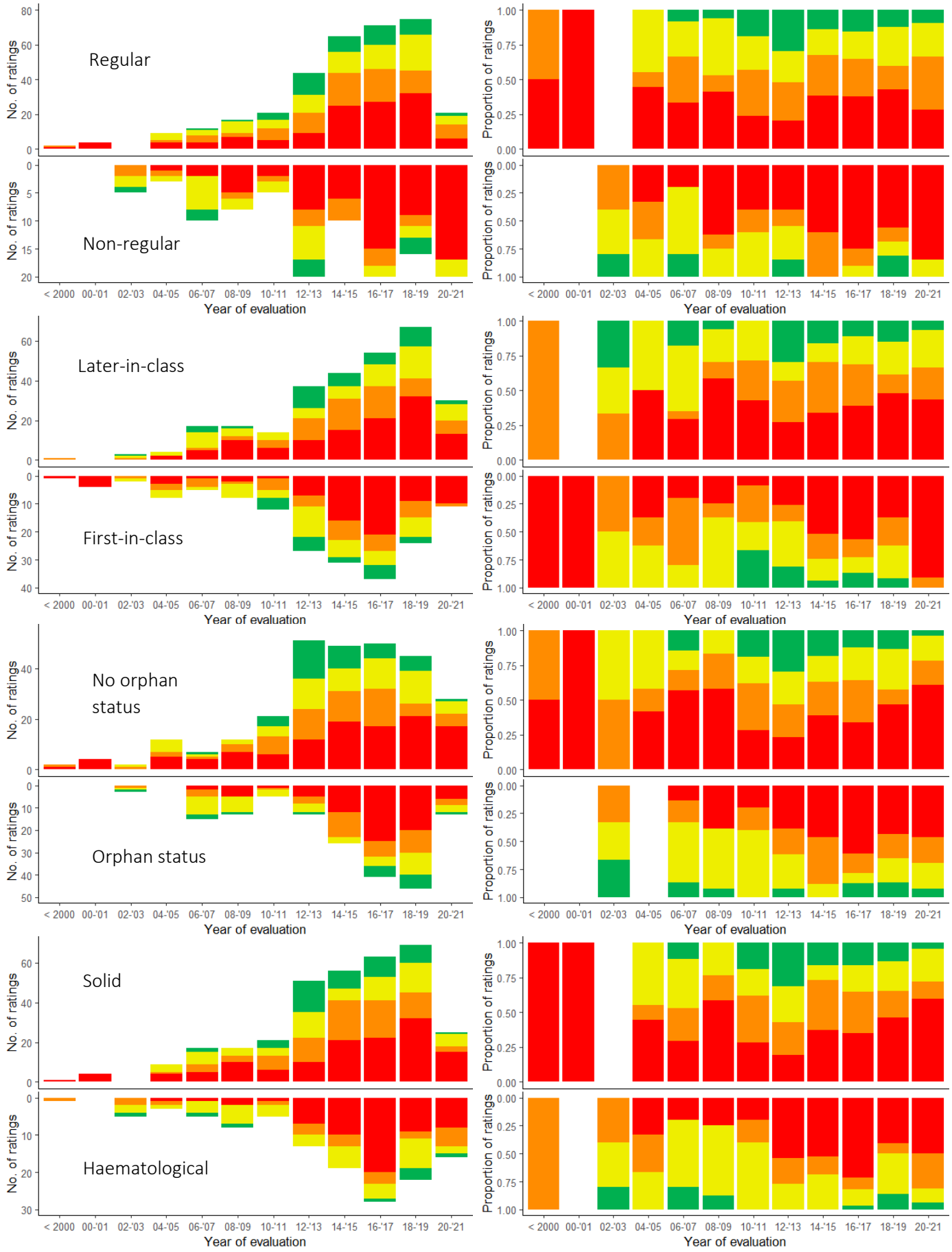
Table S3: Products from which revenue data was not available. There were 14 products (indicated in bold) from which revenue data were not available while it was specifically stated in the financial report that only major or best-selling products were reported. Thus, these 14 products were considered as missing minor products.

Company	No. products missing	Missing products (approval year)	Reason for missing data
Novartis	2	Atrience (2007), Rydapt (2017)	Not specified
Adienne	1	Phelinun (2020)	No reports available
Pfizer	**7**	**Torisel (2007), Besponsa (2017), Mylotarg (2018), Vizimpro (2019), Lorviqua (2019), Talzenna (2019), Daurismo (2020)**	**Only major products reported**
Amgen	1	Imlygic (2015)	Not specified
AOP Orphan Pharmaceuticals	1	Besremi (2019)	No reports available
Bayer AG	**1**	**Vitrakvi (2019)**	**Only 'best-selling products' reported**
Belpharma	1	Beromun (1999)	No reports available
Biolitec	1	Foscan (2001)	No reports available
Boehringer Ingelheim	2	Giotrif (2013), Vargatef (2014)	No reports available
Eisai GmbH	**2**	**Panretin (2000), Targretin (2001)**	**Only major products reported**
EUSA Pharma	2	Qarziba (2017), Fotivda (2017)	No reports available
Ferring Pharmaceuticals	1	Firmagon (2009)	No reports available
Genzyme Europe	3	MabCampath (2001), Evoltra (2006), Caprelsa (2012)	No reports available
Helsinn Birex Pharmaceuticals	1	Ledaga (2017)	No reports available
HRA Pharma Rare Diseases	1	Lysodren (2004)	No reports available
Les Laboratoires Servier	**2**	**Pixuvri (2012), Lonsurf (2016)**	**Only Top-6 reported**
Lipomed GmbH	1	Litak (2004)	No reports available
Medac Gesellschaft	1	Spectrila (2016)	No reports available
Neovii Biotech GmbH	1	Removab (2009)	No reports available
Nordic Group B.V.	1	Teysuno (2011)	No reports available
Norton Healthcare Ltd.	1	Paxene (1999)	No reports available
Nova Laboratories Ireland Limited	1	Xaluprine (2012)	No reports available
Noventia Pharma Srl	1	Ceplene (2008)	No reports available
Oasmia Pharmaceutical AB	1	Apealea (2018)	No reports available
Pierre Fabre Medicament	2	Javlor (2009), Nerlynx (2018)	No reports available
Secura Bio Limited	1	Farydak (2015)	No reports available
STEBA Biotech S.A	1	Tookad (2017)	No reports available
Sun Pharmaceutical Industries Europe	1	Odomzo (2015)	No specific product sales are reported
Teva B.V.	**2**	**Myocet (2000), Trisenox (2002)**	**Only major products reported**
Therakind (Europe) Ltd	1	Jylamvo (2017)	No reports available

Other remarks:

- Tafinlar (2013) and Mekinist (2014) were excluded from the study cohort, as revenues were only reported for the products as a combination.
- Cometriq is marketed by Ipsen Pharma and Exelis. Only data from Ipsen Pharma was available.
- Braftovi and Mektovi marketed by Pfizer and Pierre Fabre Medicament. Only data from Pfizer was available.

Annex VI: Subgroup analysis AB whole study cohort



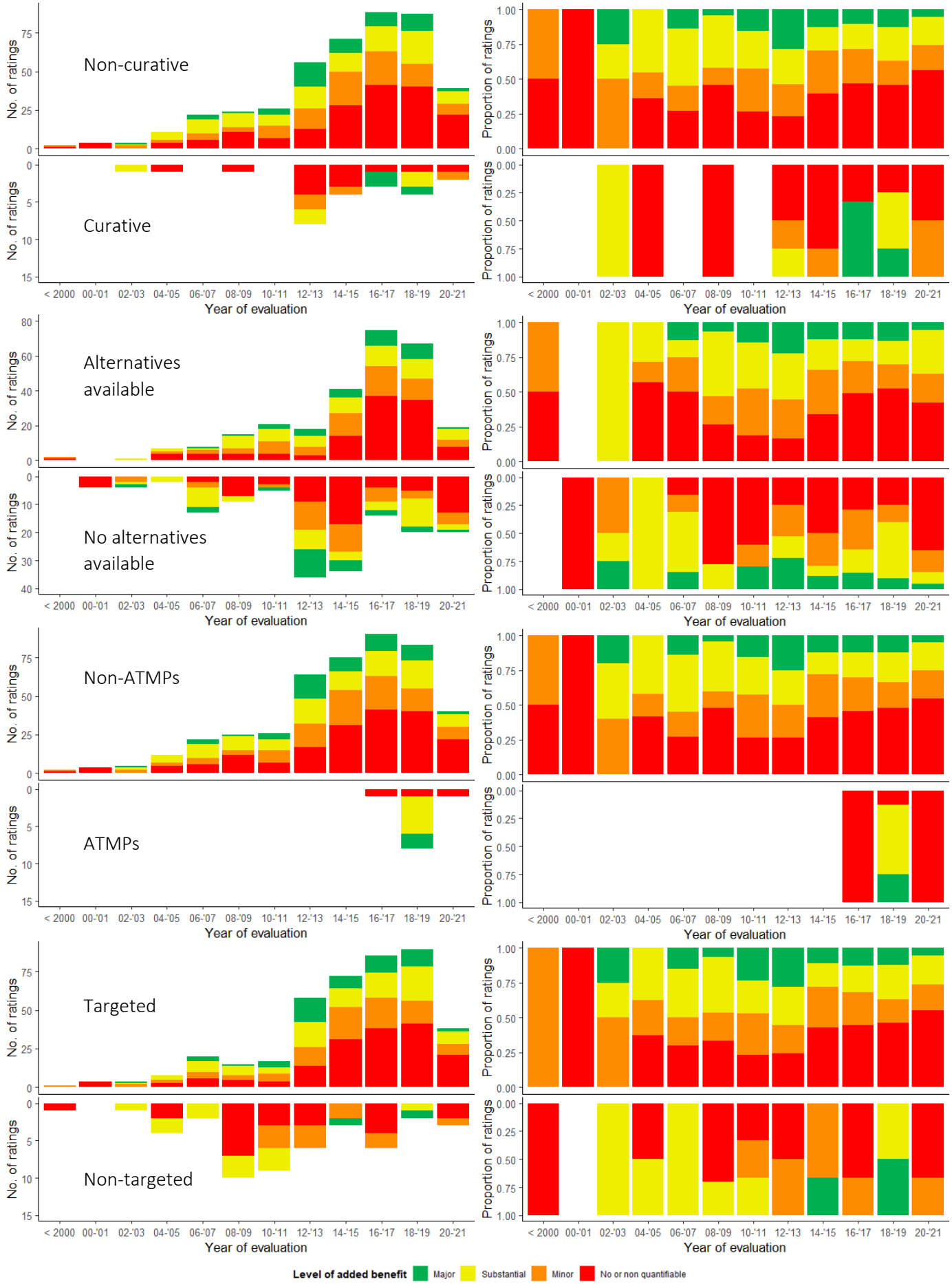


Figure S1-S8: AB ratings over time of the included subgroups with regard to all acquired ratings (*n* = 458).

Annex VII: Subgroup analysis AB HTA agencies and Prescrire

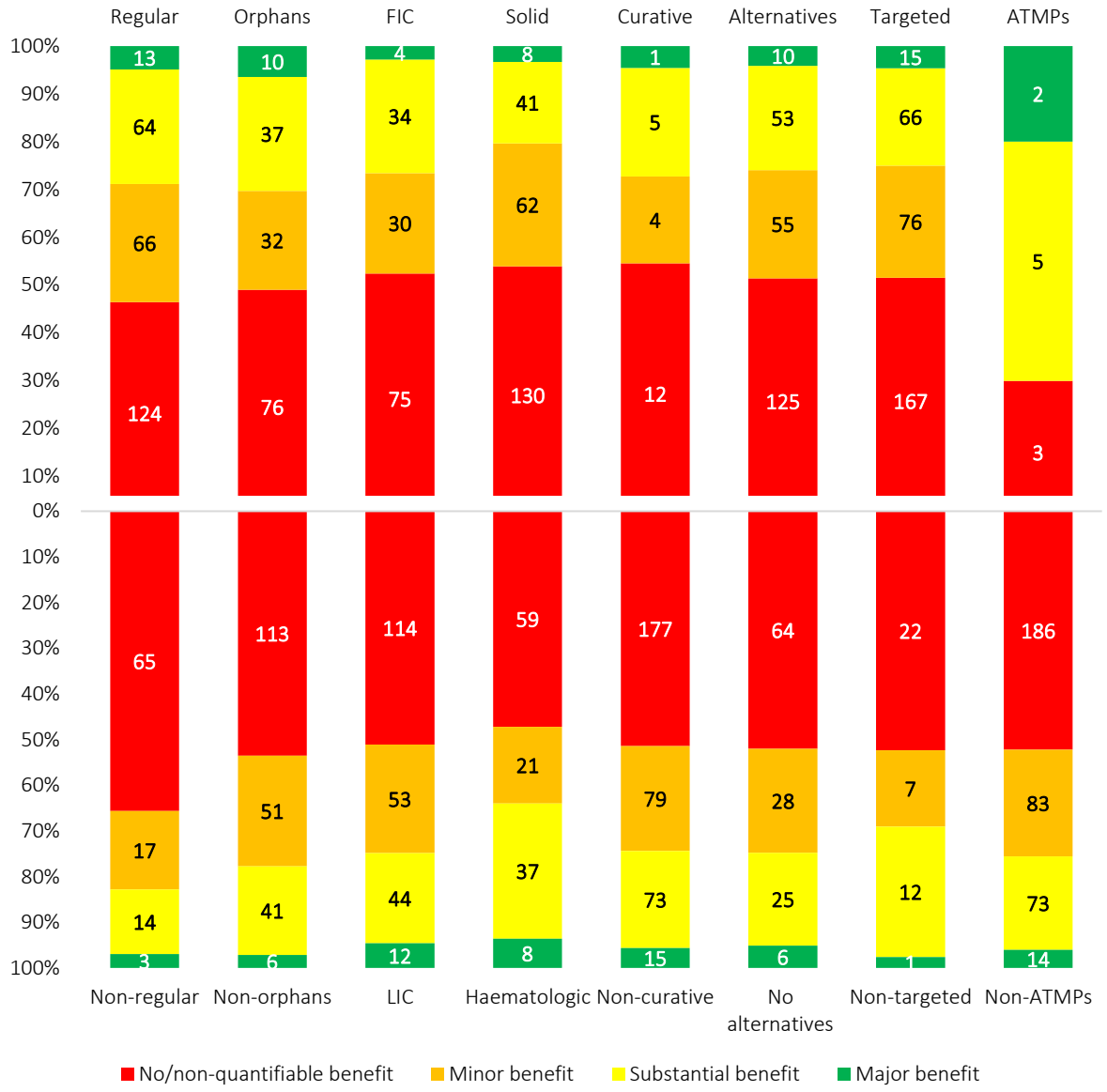


Figure S9: Distribution of the AB ratings of the subgroups in the HTA agencies and Prescrire cohort among the levels of AB.

Table S4: Risk Ratios (RRs) and 95% confidence intervals (CIs) of the included subgroups with regard to the AB ratings of the HTA agencies and Prescrire. Statistically significant results are indicated in bold.

Subgroup	AB	No AB	Proportion no AB	Risk ratio	95% CI
Non-regular approvals	34	65	0.66	**1.41**	**[1.17 -1.71]**
Regular approvals	143	124	0.46		
FIC	68	75	0.52	1.03	[0.84 – 1.26]
LIC	109	114	0.51		
Orphan	79	76	0.49	0.92	[0.75 – 1.12]
Non-orphan	98	113	0.54		
FIC	68	75	0.52	1.03	[0.84 – 1.26]
LIC	109	114	0.51		
Solid	111	130	0.54	1.14	[0.92 – 1.42]

Haematological	66	59	0.47		
Curative	10	12	0.55	1.06	[0.71 -1.57]
Non-curative	167	177	0.51		
No alternatives available	59	64	0.52	1.01	[0.82 -1.25]
Alternatives available	118	125	0.51		
ATMPs	7	3	0.30	0.57	[0.22 -1.49]
Non-ATMPs	170	186	0.52		
Targeted	157	167	0.52	0.98	[0.72 – 1.34]
Non-targeted	20	22	0.52		

In Figures S10-S16, bar charts are shown that display the AB ratings of the included subgroups over time with regard to the HTA agencies and Prescrire. The hypotheses of each of the subgroups are given in Annex III. Below, elaborations on the time trend in each subgroup are provided.

Regular vs non-regular: The 267 evaluations of regular approvals were compared to 99 evaluations of non-regular approvals. Figure S10 shows that non-regular approvals were not often rated as having major benefit; this was only the case for 3 evaluations (3%), whereas 13 of the regular approvals (5%) were classified as major benefit. Furthermore, 65 evaluations (66%) were rated as no/non-quantifiable added benefit in the non-regular subgroup, compared to 124 (46%) in the regular subgroup. Since 2012 non-regular approvals are primarily and increasingly being rated as having no/non-quantifiable added benefit. The distribution of regular approvals on the other hand, is more constantly distributed amongst the four levels of added benefit over the years.

First-in-class vs later-in-class: There were 143 evaluations for first-in-class indications and 223 for later-in-class indications in the cohort. Figure S11 show that the LIC indications include relatively more ratings that are classified as major benefit (*n* = 12, 5%) compared to the FIC indications (*n* = 4, 3%), even though this difference is small. Furthermore, the proportion of ratings classified as no-/non-quantifiable benefit was more or less the same; 75 indications (52%) in the FIC group, opposed to 114 (51%) in the LIC group. Figure S11 shows that the time trend in both subgroups is relatively similar.

Orphans vs non-orphans: There were 155 evaluations for orphan drugs, compared to 211 for non-orphan drugs. Figure S12 shows that the distribution amongst levels of AB is relatively similar in the two subgroups over time. Overall, 113 evaluations (54%) had been classified as no/non-quantifiable AB in the group without orphan designation, compared to 76 (49%) in the group with orphan designation. Furthermore, a slightly larger proportion of the evaluations had been rated as major benefit in the orphan group (*n* = 10, 6%) compared to the non-orphan group (*n* = 6, 3%).

Solid vs haematological malignancies: There were 241 ratings for indications of solid malignancies compared to 125 for haematological malignancies. In both subgroups, eight indications were classified as major benefit, which

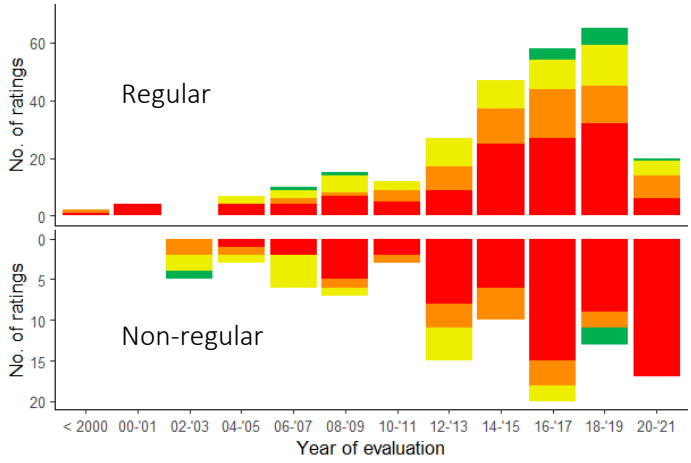
corresponds to 3% and 6% for the solid and haematological subgroups, respectively. Regarding indications classified as no/non-quantifiable AB, these include 130 evaluations (54%) in the solid subgroup, compared to 59 (47%) in the haematological subgroup. The proportion of no/non-quantifiable ratings increases in both subgroups over the years, although to a lesser extent in the solid subgroup (see Figure S13). All in all, both the distribution amongst the levels of AB, as well as the development over time, are rather similar in both subgroups.

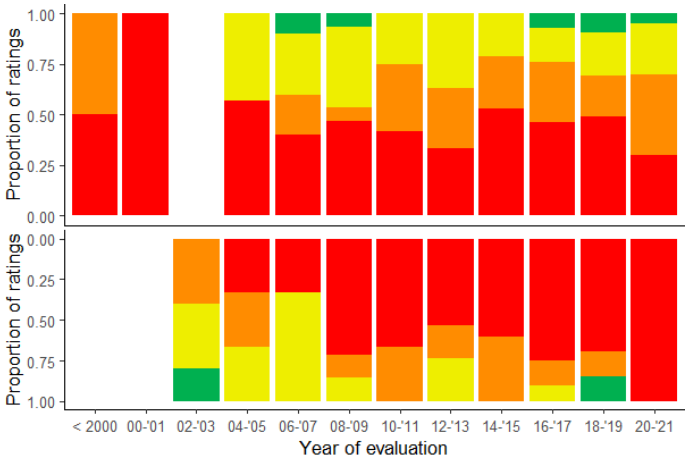
Curative vs non-curative: There were 22 evaluations of curative indications and 344 of non-curative indications. Thus, the two subgroups differ considerably in sample size, see Figure S14. Only one of the ratings for curative indications (5%) was classified as major benefit, opposed to 15 ratings (4%) in the non-curative subgroup. Furthermore, 12 evaluations (55%) have been classified as no/non-quantifiable AB in the curative cohort, compared to 177 (51%) in the non-curative cohort. The notable difference in sample sizes complicates drawing firm conclusions.

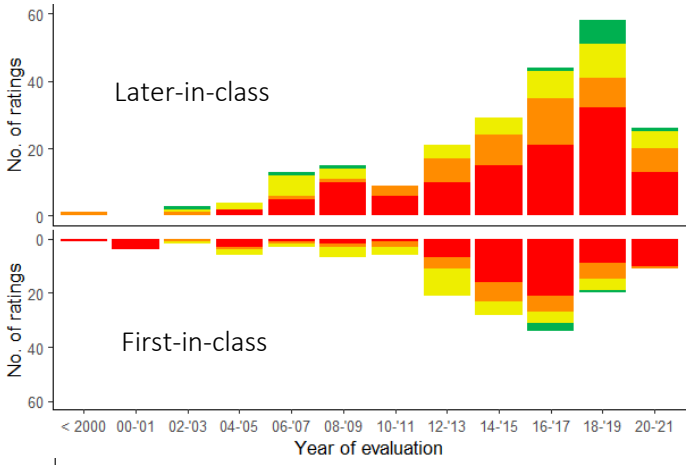
Alternatives available vs no alternatives available: Evaluations of treatments with alternatives available (*n* = 243) were compared to treatments without alternatives (*n* = 123) (Figure S15). In the subgroup without alternatives available, 6 ratings (5%) were classified as major benefit, compared to 10 (4%) in the other subgroup. Furthermore, 64 (52%) ratings were classified as no/non-quantifiable benefit in the group without alternatives, whereas this was 125 (51%) in the group with alternatives available. There is not a clear difference in the trends of both subgroups.

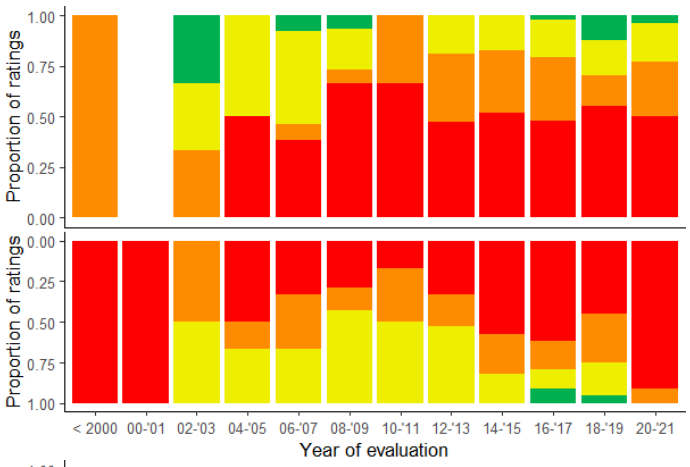
ATMPs vs non-ATMPs: Evaluations of ATMP therapies (*n* = 10) were compared to those of non-ATMP therapies (*n* = 356). As can be seen from Figure S16, the first group is only small and have only been available since a few years. The small amount of ratings are therefore clustered between 2016-2021, which makes it not possible to draw conclusions on the differences in trends of both subgroups.

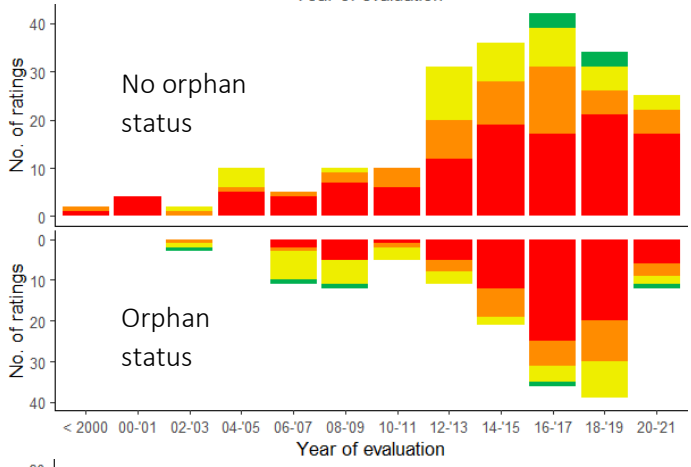
Targeted vs non-targeted: Ratings of targeted indications (*n* = 324) were compared to those of non-targeted indications (*n* = 42) over time. As can be seen in Figure S17, only one non-targeted indication (2%) had been classified as major benefit, compared to 15 indications (5%) in the targeted subgroup. With regard to indications rated as no/non-quantifiable AB, there are 22 indications (52%) in the non-targeted subgroup, compared to 167 (51%) in the targeted subgroup. Furthermore, for both subgroups, the proportion of no/non-quantifiable AB stays relatively constant over the years.

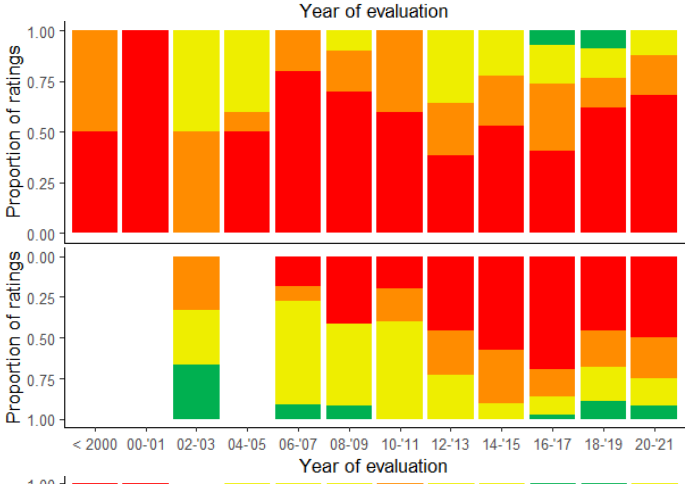

Regular
No. of ratings
Non-regular
No. of ratings
< 2000 00-'01 02-'03 04-'05 06-'07 08-'09 10-'11 12-'13 14-'15 16-'17 18-'19 20-'21
Year of evaluation

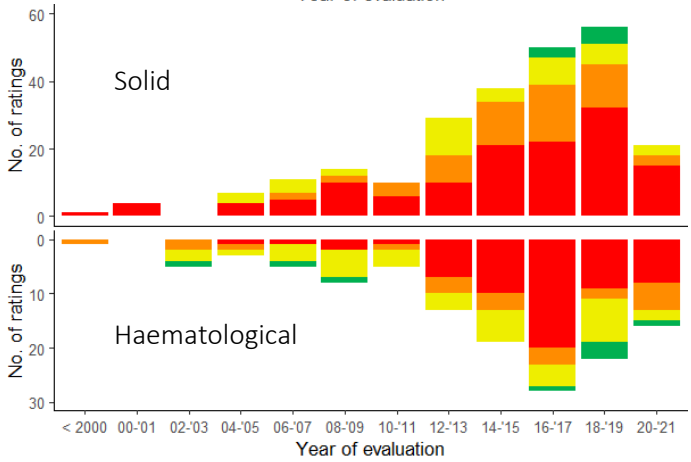

Proportion of ratings
Proportion of ratings
< 2000 00-'01 02-'03 04-'05 06-'07 08-'09 10-'11 12-'13 14-'15 16-'17 18-'19 20-'21
Year of evaluation

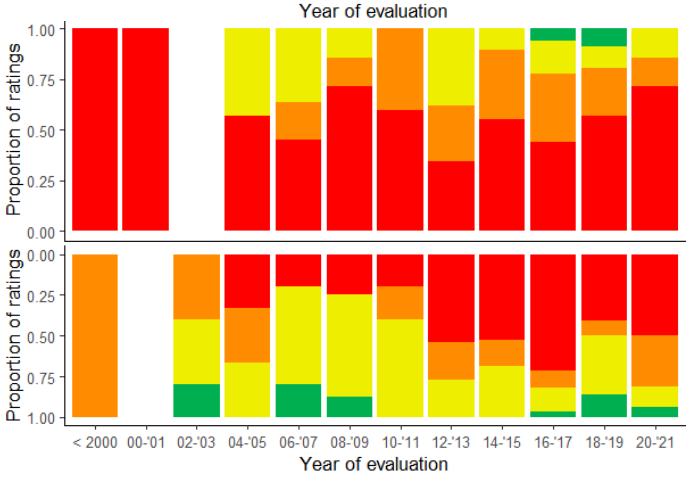

Later-in-class
No. of ratings
First-in-class
No. of ratings
< 2000 00-'01 02-'03 04-'05 06-'07 08-'09 10-'11 12-'13 14-'15 16-'17 18-'19 20-'21
Year of evaluation


Proportion of ratings
Proportion of ratings
< 2000 00-'01 02-'03 04-'05 06-'07 08-'09 10-'11 12-'13 14-'15 16-'17 18-'19 20-'21
Year of evaluation


No orphan status
No. of ratings
Orphan status
No. of ratings
< 2000 00-'01 02-'03 04-'05 06-'07 08-'09 10-'11 12-'13 14-'15 16-'17 18-'19 20-'21
Year of evaluation


Proportion of ratings
Proportion of ratings
< 2000 00-'01 02-'03 04-'05 06-'07 08-'09 10-'11 12-'13 14-'15 16-'17 18-'19 20-'21
Year of evaluation


Solid
No. of ratings
Haematological
No. of ratings
< 2000 00-'01 02-'03 04-'05 06-'07 08-'09 10-'11 12-'13 14-'15 16-'17 18-'19 20-'21
Year of evaluation


Proportion of ratings
Proportion of ratings
< 2000 00-'01 02-'03 04-'05 06-'07 08-'09 10-'11 12-'13 14-'15 16-'17 18-'19 20-'21
Year of evaluation

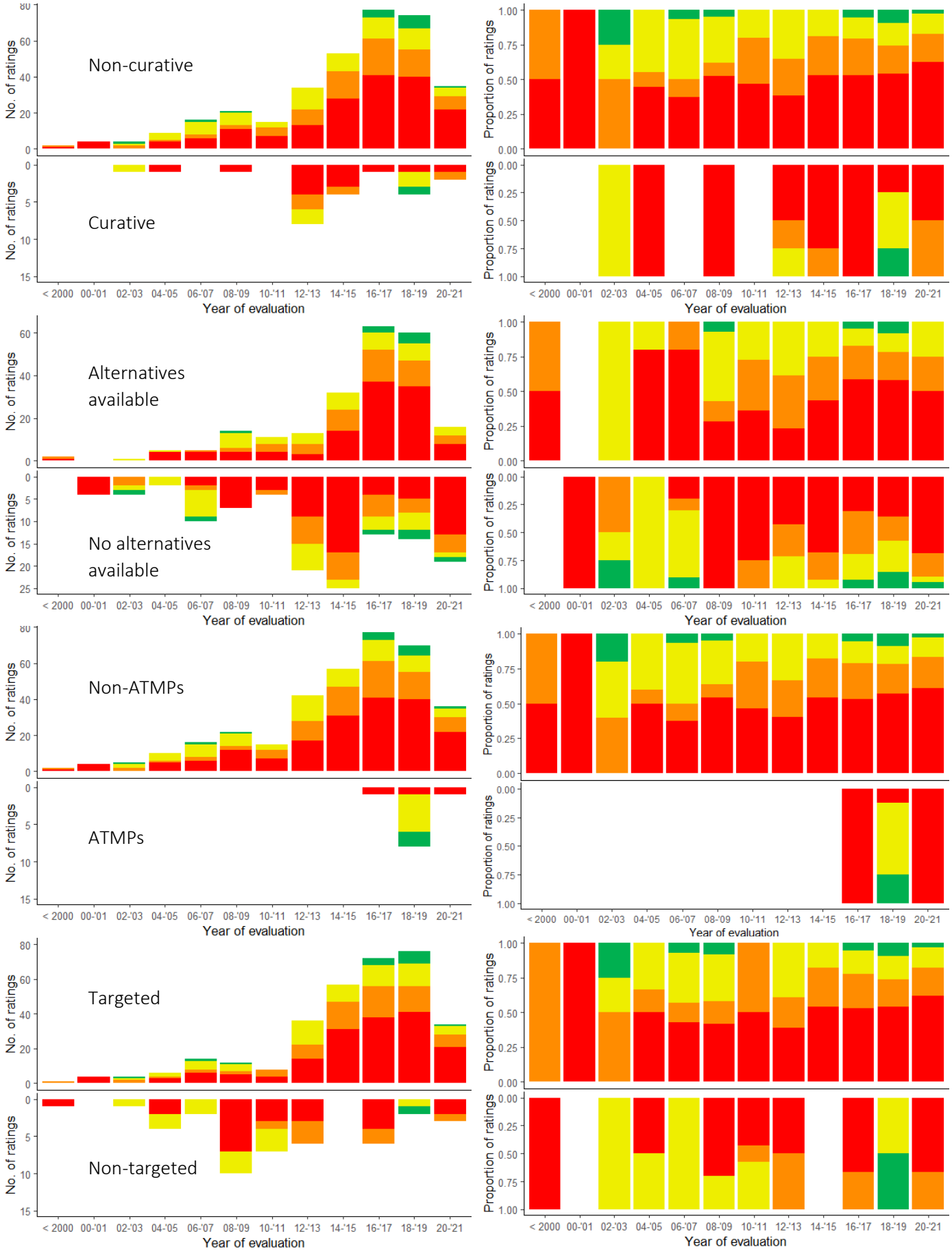


Figure S10-S17: AB ratings over time of the included subgroups with regard to the HTA agencies and Prescrire (*n* = 366).

Annex VIII: Subgroup analysis AB ESMO and ASCO

Figure S18: Distribution of the AB ratings of the subgroups in the ESMO and ASCO cohort among the levels of AB.

Table S5: RRs and 95% CIs of the included subgroups with regard to the AB ratings of the ESMO and ASCO. Statistically significant results are indicated in bold.

Subgroup	Low AB	High AB	Proportion low AB	Risk ratio	95% CI
Non-regular approvals	0	18	0	0.10	[0.01 – 1.52]
Regular approvals	20	54	0.27		
FIC	5	22	0.19	0.80	[0.32 – 1.99]
LIC	15	50	0.23		
Orphan	7	13	0.35	1.94	[0.89 – 4.20]
Non-orphan	13	59	0.18		
Curative	0	2	0	0.74	[0.06 – 9.56]
Non-curative	20	70	0.22		
No alternatives available	9	29	0.24	1.16	[0.53 – 2.53]
Alternatives available	11	43	0.20		
Targeted	16	71	0.18	**0.23**	**[0.12 – 0.43]**
Non-targeted	4	1	0.80		

In Figures S19-S22, bar charts are shown in which the subgroups regarding the ESMO and ASCO cohort are compared. Similarly to the previous AB analysis, hypotheses of all subgroups can be found in Annex III. Last, a few subgroups were left out in this analysis, since some sample sizes were too small to make meaningful comparisons. Since there were no ATMP indications and no indications for haematological malignancies included in the cohort, these subgroups are left out. Furthermore, there were five or less ratings of curative and non-targeted indications, making us unable to analyze the corresponding subgroups.

Regular vs non-regular: Evaluations of regular approvals (*n* = 74) were compared to those of non-regular approvals (*n* = 18). Of the first group, 37 ratings (50%) were classified as major benefit, compared to six ratings (34%) in the non-regular group. Furthermore, the regular approvals contained 20 ratings (27%) of minor AB, whereas the non-regular group contained none. A robust time trend cannot be identified due to the small sample size of the non-regular subgroup, as can be seen in Figure S19.

First-in-class vs later-in-class: Evaluations of FIC indications (*n* = 27) were compared to those of LIC indications (*n* = 65), see Figure S20. In the FIC group, 14 evaluations (52%) were classified as major benefit, whereas this was 29 evaluations (45%) in the LIC group. Regarding the lowest level of AB, 5 ratings (19%) were classified as minor AB in the FIC group, compared to 15 (23%) in the LIC group. The lowest ratings of the FIC group are mainly centered around the period between 2004 and 2011, whereas this is between 2008 and 2017 in the LIC group. For both groups, the proportion of major AB ratings has been decreasing over time since 2012 – 2013, whilst simultaneously the proportion of substantial AB ratings are increasing.

Orphans vs non-orphans: Ratings of indications with initial orphan designation (*n* = 20) were compared to those without (*n* = 72). In the orphan subgroup, seven ratings (35%) were classified as major AB, compared to 36 (50%) in the non-orphan subgroup. Furthermore, seven evaluations of orphan indications (35%) were classified as minor benefit, compared to 13 (18%) in the non-orphan group. Regarding the development of ratings over time, the proportion of major and minor AB ratings in the non-orphan group seem to decrease over time, whereas the proportion of substantial AB ratings increases. A robust time trend in the non-orphan subgroup cannot be allocated, due to the small sample size (see Figure S21).

Alternatives available vs no alternatives available: There were 54 evaluations of indications with alternative treatments, compared to 38 evaluations of indications without alternative treatment (see Figure S22). Of the first group, 26 ratings (48%) were classified as major benefit, and 11 (20%) as minor benefit. In the subgroup without alternatives, this was 17 (45%) and nine (24%) regarding major- and minor AB, respectively. Thus, these proportions are very similar amongst the two groups. There are no striking differences between both groups with regard to the time trend.

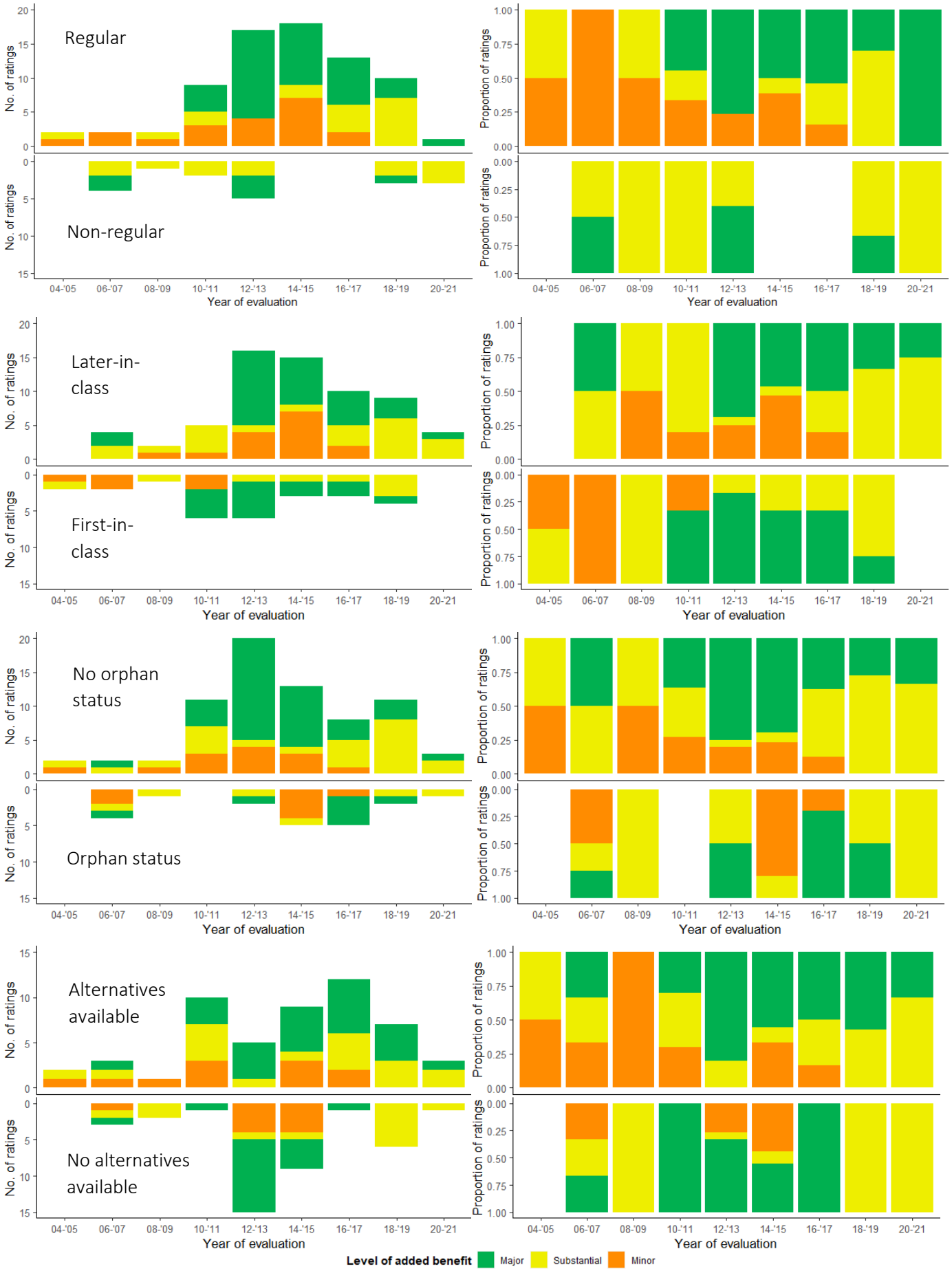


Figure S19-S22: AB ratings over time of the included subgroups with regard to ESMO and ASCO (*n* = 92).

Annex IX: AB individual agencies over time

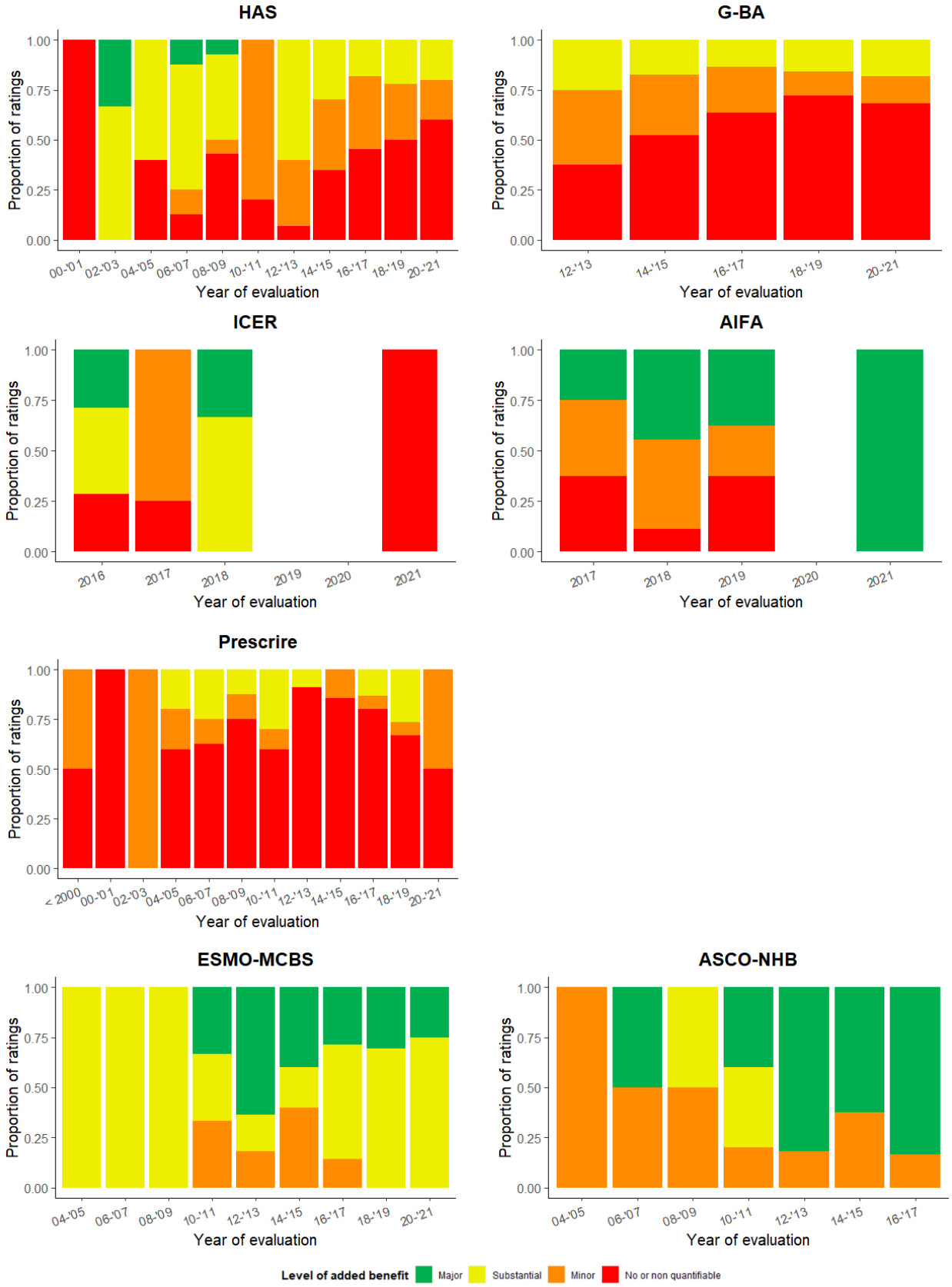


Figure S23-S29: Proportional bar charts of the acquired AB ratings of each individual agency over time.

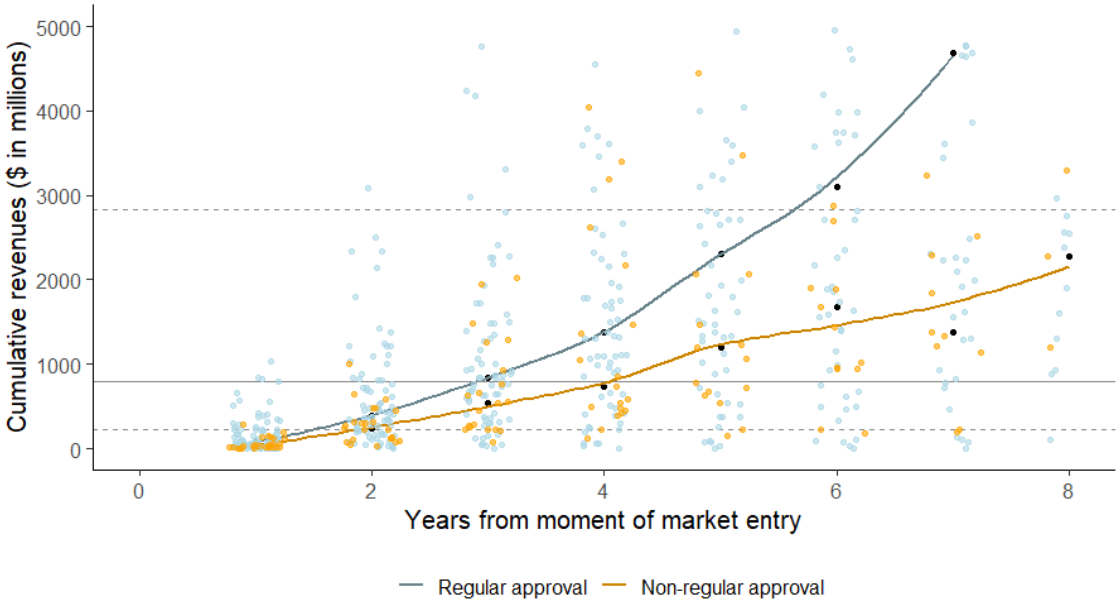
Table S6: RRs and 95% CIs of the included subgroups with regard to the AB ratings of each individual agency. Statistically significant results are indicated in bold.

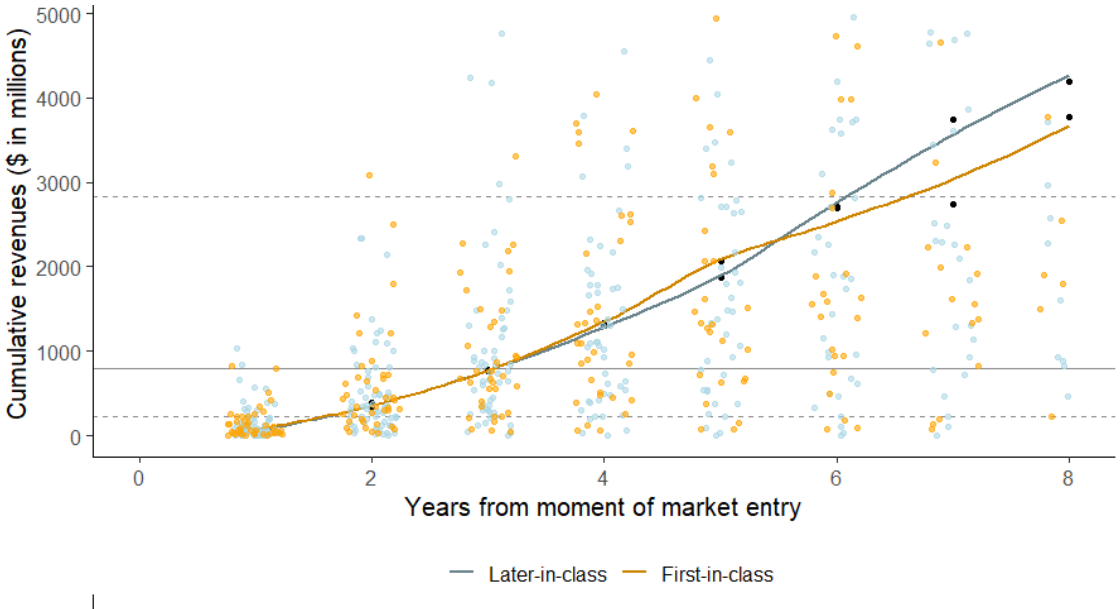
Agency	Subgroup	AB	No AB	Proportion no AB	Risk ratio	95% CI
HAS	Non-regular approvals	18	13	0.42	1.24	[0.75 - 2.07]
	Regular approvals	57	29	0.34		
	Orphan	34	14	0.29	0.72	[0.43 - 1.22]
	Non-orphan	41	28	0.41		
	FIC	35	12	0.26	0.60	[0.34 - 1.04]
	LIC	40	30	0.43		
	Solid	48	31	0.39	1.36	[0.77 - 2.39]
	Haematological	27	11	0.29		
	Curative	5	2	0.29	0.79	[0.24 - 2.60]
	Non-curative	70	40	0.36		
	No alternatives available	25	18	0.42	1.29	[0.80 - 2.09]
	Alternatives available	50	24	0.32		
	Targeted	67	33	0.33	0.62	[0.37 - 1.06]
	Non-targeted	8	9	0.53		
	ATMPs	1	0	0	0.69	[0.06 - 7.68]
	Non-ATMPs	74	42	0.36		
G-BA	Non-regular approvals	5	23	0.82	1.56	[1.19 - 2.05]
	Regular approvals	38	42	0.53		
	Orphan	11	28	0.72	1.34	[1.00 - 1.80]
	Non-orphan	32	37	0.54		
	FIC	15	28	0.65	1.14	[0.84 - 1.55]
	LIC	28	37	0.57		
	Solid	33	38	0.54	0.73	[0.55 - 0.98]
	Haematological	10	27	0.73		
	Curative	2	6	0.75	1.27	[0.83 - 1.96]
	Non-curative	41	59	0.59		
	No alternatives available	17	17	0.50	0.77	[0.53 - 1.12]
	Alternatives available	26	48	0.65		
	Targeted	39	62	0.61	1.43	[0.60 - 3.42]
	Non-targeted	4	3	0.43		
	ATMPs	0	3	1	1.69	[1.44 - 1.99]
	Non-ATMPs	43	62	0.59		
ICER	Non-regular approvals	1	3	0.75	**8.25**	**[1.17 – 58.14]**
	Regular approvals	10	1	0.09		
	Orphan	7	4	0.36	3.75	[0.24 – 57.45]
	Non-orphan	4	0	0		
	FIC	3	2	0.40	2.0	[0.39 - 10.31]
	LIC	8	2	0.20		
	Solid	6	1	0.14	0.38	[0.05 – 2.88]
	Haematological	5	3	0.38		
	Curative	1	0	0	0.83	[0.07 – 103.77]
	Non-curative	10	4	0.29		
	No alternatives available	2	1	0.33	1.33	[0.20 - 8.71]
	Alternatives available	9	3	0.25		
	ATMPs	2	0	0	0.52	[0.04 – 7.28]

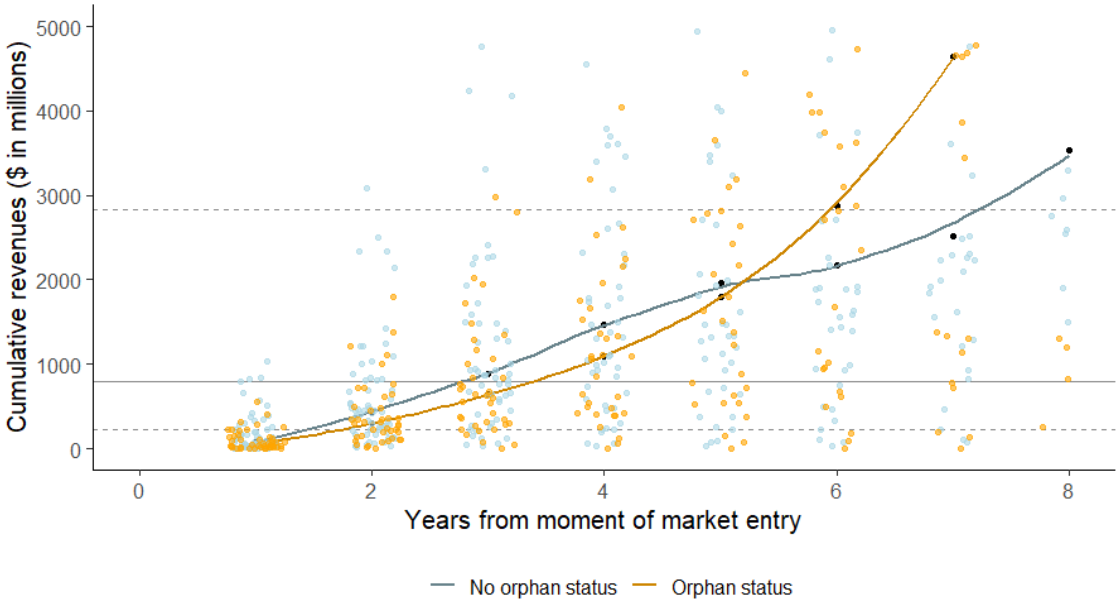
	Non-ATMPs	9	4	0.31		
AIFA	Non-regular approvals	3	3	0.50	2.50	[0.76 - 8.19]
	Regular approvals	16	4	0.20		
	Orphan	12	3	0.20	0.55	[0.15 – 1.98]
	Non-orphan	7	4	0.36		
	FIC	6	3	0.33	1.42	[0.40 – 5.00]
	LIC	13	4	0.24		
	Solid	13	5	0.28	1.11	[0.27 - 4.56]
	Haematological	6	2	0.25		
	Curative	1	0	0	0.87	[0.07 - 10.30]
	Non-curative	18	7	0.28		
	No alternatives available	3	2	0.40	1.68	[0.45 - 6.28]
	Alternatives available	16	5	0.24		
	Targeted	18	7	0.28	1.15	[0.10 - 13.71]
	Non-targeted	1	0	0		
	ATMPs	2	0	0	0.56	[0.04 - 7.48]
	Non-ATMPs	17	7	0.29		
Prescrire	Non-regular approvals	7	23	0.77	1.12	[0.87 - 1.44]
	Regular approvals	22	48	0.69		
	Orphan	15	27	0.64	0.85	[0.65 - 1.11]
	Non-orphan	14	44	0.76		
	FIC	9	30	0.77	1.14	[0.90 – 1.46]
	LIC	20	41	0.67		
	Solid	11	55	0.83	**1.77**	**[1.22 - 2.57]**
	Haematological	18	16	0.47		
	Curative	1	4	0.80	1.13	[0.72 - 1.79]
	Non-curative	28	67	0.71		
	No alternatives available	12	26	0.68	0.94	[0.72 - 1.23]
	Alternatives available	17	45	0.76		
	Targeted	22	61	0.73	1.25	[0.82 - 1.90]
	Non-targeted	7	10	0.59		
	ATMPs	2	0	0	0.23	[0.02 - 2.91]
	Non-ATMPs	27	71	0.72		
Agency	**Subgroup**	**Low AB**	**High AB**	**Proportion low AB**	**Risk ratio**	**95% CI**
ESMO	Non-regular approvals	0	12	0	0.18	[0.01 - 2.86]
	Regular approvals	9	34	0.21		
	Orphan	3	8	0.27	2.00	[0.59 – 6.76]
	Non-orphan	6	38	0.14		
	FIC	1	14	0.07	0.33	[0.05 - 2.44]
	LIC	8	32	0.20		
	Curative	0	2	0	0.95	[0.07 - 12.70]
	Non-curative	9	44	0.17		
	No alternatives available	5	17	0.23	1.88	[0.57 - 6.22]
	Alternatives available	4	29	0.12		
	Targeted	6	46	0.12	**0.12**	**[0.05 - 0.24]**
	Non-targeted	3	0	1		
ASCO	Non-regular approvals	0	6	0	0.20	[0.01 - 2.99]

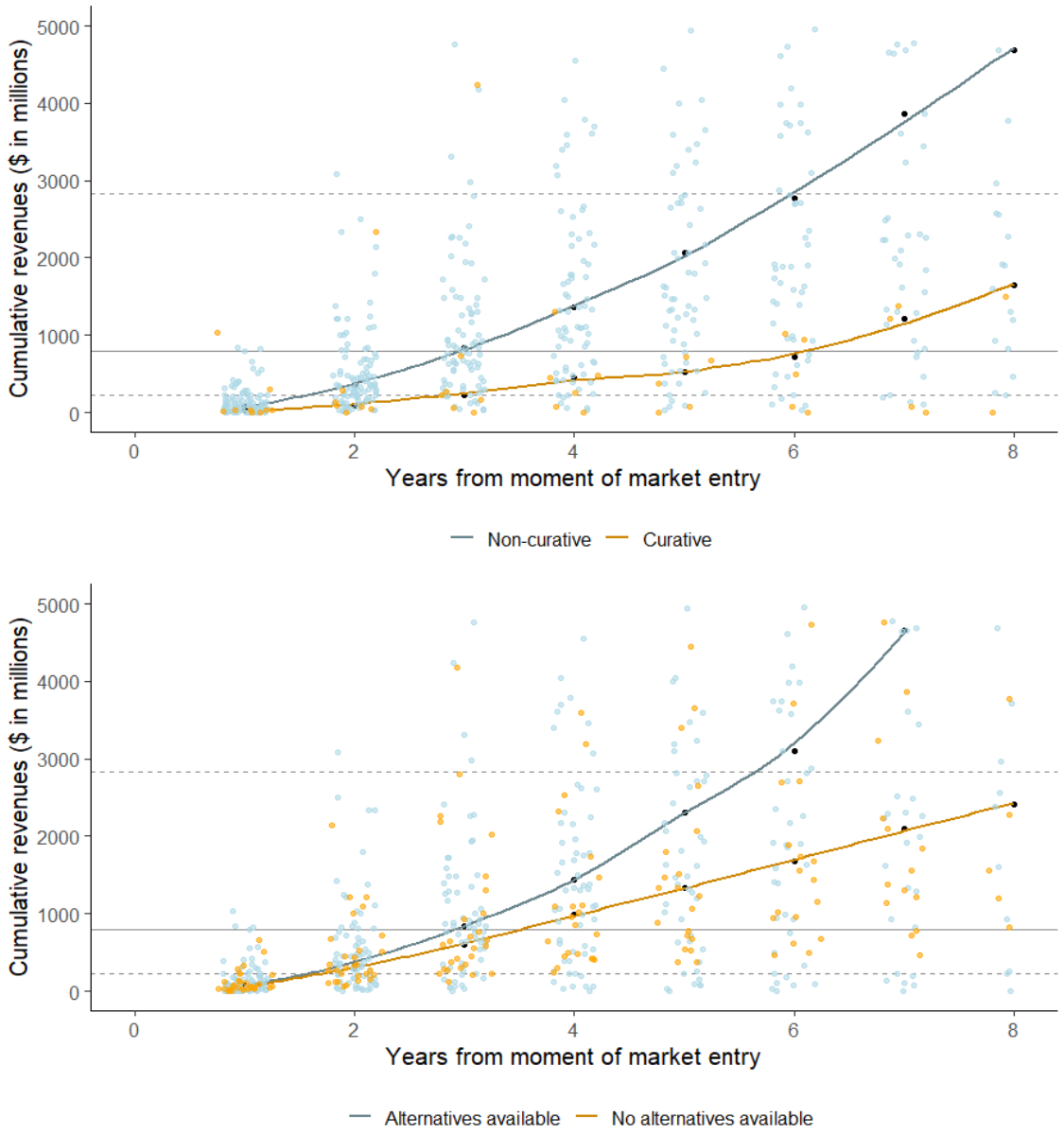
	Regular approvals	11	20	0.35		
	Orphan	4	5	0.44	1.78	[0.67 - 4.70]
	Non-orphan	7	21	0.25		
	FIC	4	8	0.33	1.19	[0.43 - 3.29]
	LIC	7	18	0.28		
	No alternatives available	4	12	0.25	0.75	[0.26 - 2.13]
	Alternatives available	7	14	0.33		
	Targeted	10	25	0.29	0.57	[0.13 - 2.51]
	Non-targeted	1	1	0.50		

Annex X: Subgroup analysis drug revenues









Figures S30-S34: First eight years of generating revenues for different subgroups.

Table S7: Number of drugs in each year from the moment of market entry of which revenue data was available.

Year	1	2	3	4	5	6	7	8
Regular approval	83	80	74	69	64	61	53	46
Non-regular approval	26	23	20	19	17	15	11	9
FIC drugs	41	40	38	37	35	33	26	21
LIC drugs	68	63	56	51	46	43	38	34
Orphan drugs	44	41	38	35	31	29	23	19
Non-orphan drugs	65	62	56	53	50	47	41	36
Curative drugs	9	7	7	7	6	6	5	4
Non-curative drugs	100	96	87	81	75	70	59	51
Alternatives available	78	74	67	64	58	55	45	37
No alternatives available	31	29	27	24	23	21	19	18

Table S8: Median cumulative revenues at year 3 and year 5 from the moment of market entry of the included subgroups.

Subgroup	Median cumulative revenues at year 3 ($ in millions)	Median cumulative revenues at year 5 ($ in millions)
Regular approvals	840.6	2301.1
Non-regular approvals	544.3	1195.9
FIC drugs	762.9	2068.6
LIC drugs	783.9	1873.4
Orphan drugs	640.2	1793.5
Non-orphan drugs	877.2	1958.0
Curative drugs	229.9	519.9
Non-curative drugs	833.8	2068.6
Alternatives available	844.8	2301.1
No alternatives available	602.0	1332.9

Annex XI: Association added benefit and revenues

Table S9: Result of the linear regression analyses that were performed to test the association between AB and cumulative revenues at year 3. Statistically significant results are indicated in bold.

	Revenues (increment, $ in millions)	95% CI ($ in millions)	Significance level
HAS			
Intercept (no AB) (*n* = 21)	1082	[397 – 1767]	Ref.
Minor AB (*n* = 29)	+ 554	[-346 – 1454]	0.2247
Substantial AB (*n* = 41)	+ 829	[-14 – 1671]	0.0539
Major AB (*n* = 4)	+ 1168	[-54 – 2881]	0.1790
G-BA			
Intercept (no AB) (*n* = 41)	1297	[853 – 1742]	Ref.
Minor AB (*n* = 15)	– 537	[-1396 – 322]	0.216
Substantial AB (*n* = 14)	– 23	[-904 – 858]	0.959
Major AB (*n* = 0)	NA	NA	NA
ICER			
Intercept (no AB) (*n* = 3)	992	[-438 – 2422]	Ref.
Minor AB (*n* = 0)	NA	NA	NA
Substantial AB (*n* = 10)	+ 387	[-1243 – 2017]	0.6164
Major AB (*n* = 3)	+ 1966	[-56 – 3988]	0.0558
AIFA			
Intercept (no AB) (*n* = 6)	2549	[915 – 4183]	Ref.
Minor AB (*n* = 6)	– 167	[-2478 – 2144]	0.88246
Substantial AB (*n* = 0)	NA	NA	NA
Major AB (*n* = 14)	– 1131	[-3084 – 822]	0.24321
Prescrire			
Intercept (no AB) (*n* = 65)	1574	[1184 – 1964]	Ref.
Minor AB (*n* = 14)	– 164	[-1090 – 762]	0.726
Substantial AB (*n* = 15)	+ 517	[-384 – 1417]	0.258
Major AB (*n* = 0)	NA	NA	NA
ESMO			
Intercept (Minor AB) (*n* = 10)	525	[-482 – 1533]	Ref.
Substantial AB (*n* = 18)	+ 877	[-380 – 2133]	0.1670
Major AB (*n* = 23)	+ 1440	[233 – 2647]	**0.0204**
ASCO			
Intercept (Minor AB) (*n* = 11)	1724	[585 – 2864]	Ref.
Substantial AB (*n* = 3)	– 1187	[-3649 – 1275]	0.33193
Major AB (*n* = 17)	+ 212	[-1250 – 1675]	0.76857

Table S10: Results of the linear regression for individual agencies, in which only products are considered that had one indication at the end of follow-up. Statistically significant results are indicated in bold.

	Revenues (increment, $ in millions)	95% CI ($ in millions)	Significance level
HAS			
Intercept (no AB) (*n* = 11)	711	[173 – 1249]	Ref.
Minor AB (*n* = 9)	– 90	[-892 – 712]	0.8206
Substantial AB (*n* = 12)	+ 730	[-15 – 1474]	0.0545
Major AB (*n* = 0)	NA	NA	NA
G-BA			
Intercept (no AB) (*n* = 13)	740	[276 – 1202]	Ref.
Minor AB (*n* = 7)	– 162	[-945 – 620]	0.67394
Substantial AB (*n* = 10)	+ 299	[-404 – 1001]	0.39059
Major AB (*n* = 0)	NA	NA	NA
ICER			
Intercept (no AB) (*n* = 1)	354	[-2913 – 3621]	Ref.
Minor AB (*n* = 0)	NA	NA	NA
Substantial AB (*n* = 5)	+ 892	[-2687 – 4471]	0.527

Major AB (*n* = 1)	+ 1912	[-2708 – 6532]	0.315
AIFA			
Intercept (no AB) (*n* = 2)	1988	[-275 – 4251]	Ref.
Minor AB (*n* = 1)	– 1180	[-5099 – 2739]	0.5072
Substantial AB (*n* = 0)	NA	NA	NA
Major AB (*n* = 8)	– 800	[-3330 – 1730]	0.4867
Prescrire			
Intercept (no AB) (*n* = 23)	662	[354 – 970]	Ref.
Minor AB (*n* = 7)	– 36	[-674 – 601]	0.908213
Substantial AB (*n* = 4)	+ 1827	**[1027 – 2628]**	**5.75e-05**
Major AB (*n* = 0)	NA	NA	NA
ESMO			
Intercept (Minor AB) (*n* = 5)	406	[-503 – 1316]	Ref.
Substantial AB (*n* = 5)	+ 16	[-1270 – 1302]	0.9790
Major AB (*n* = 13)	+ 922	[-148 – 1992]	0.0874
ASCO			
Intercept (Minor AB) (*n* = 3)	555	[-276 – 1386]	Ref.
Substantial AB (*n* = 2)	+ 126	[-1187 – 1439]	0.833
Major AB (*n* = 7)	+ 442	[-551 – 1435]	0.340

References

1. Haute Autorité de Santé. Methods and criteria for assessing medicinal products. Available from: https://www.has-sante.fr/jcms/c_2035651/en/methods-and-criteria-for-assessing-medicines. Accessed March 1, 2021.
2. Wenzl M, Paris V. Pharmaceutical Reimbursement and Pricing in Germany. OECD. June 2018. Available from: https://www.oecd.org/health/health-systems/Pharmaceutical-Reimbursement-and-Pricing-in-Germany.pdf. Accessed March 1, 2021.
3. ICER. Working Towards Fair Pricing, Fair Access, & Future Innovation. Available from: https://icer.org/. Accessed March 1, 2021.
4. Salas-Vega S, Shearer E, Mossialos E. Relationship between costs and clinical benefits of new cancer medicines in Australia, France, the UK, and the US. *Soc Sci Med*. 2020;258:113042.
5. Italian Medicines Agency. Mission and values. Available from: https://www.aifa.gov.it/en/web/guest/mission. Accessed March 1, 2021.
6. Prescrire. Who are we? Available from: https://english.prescrire.org/en/82/169/0/0/About.aspx. Accessed March 1, 2021.
7. Vivot A, Jacot J, Zeitoun JD, Ravaud P, Crequit P, Porcher R. Clinical benefit, price and approval characteristics of FDA-approved new drugs for treating advanced solid cancer, 2000-2015. *Ann Oncol Off J Eur Soc Med Oncol*. 2017;28(5):1111–6.
8. European Medicines Agency. Piqray. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/piqray. Accessed August 27, 2021.
9. Gemeinsamer Bundesausschusses. Arzneimittel-Richtlinie/Anlage XII: Alpelisib in Kombination mit Fulvestrant (Mammakarzinom mit PIK3CA-Mutation, HR+, HER2-, Kombination mit Fulvestrant). Available from: https://www.g-ba.de/beschluesse/4706/. Accessed August 27, 2021.
10. European Medicines Agency. Kymriah. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/kymriah. Accessed August 27, 2021.
11. Italian Medicines Agency. Innovative medicinal products. Available from: https://www.aifa.gov.it/en/farmaci-innovativi. Accessed August 27, 2021.
12. Cherny NI, de Vries EGE, Dafni U, Garrett-Mayer E, McKernin SE, Piccart M, et al. Comparative assessment of clinical benefit using the ESMO-magnitude of clinical benefit scale version 1.1 and the ASCO Value Framework Net Health Benefit score. *J Clin Oncol*. 2019;37(4):336–49.
13. ESMO. ESMO-MCBS Scorecards. Available from: https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-scorecards. Accessed March 3, 2021.
14. European Medicines Agency. Guideline on the scientific application and the practical arrangements necessary to implement the procedure for accelerated assessment pursuant to Article 14(9) of Regulation (EC) No 726/2004. Available from: https://www.ema.europa.eu/en/guideline-scientific-application-practical-arrangements-necessary-implement-procedure-accelerated. Accessed Spetember 15, 2021.
15. Molto C, Hwang TJ, Borrell M, Andres M, Gich I, Barnadas A, et al. Clinical benefit and cost of breakthrough cancer drugs approved by the US Food and Drug Administration. *Cancer*. 2020;126(19):4390–9.
16. Fregonese L, Greene L, Hofer M, Magrelli A, Naumann-Winter F, Larsson K, et al. Demonstrating significant benefit of orphan medicines: analysis of 15 years of experience in Europe. *Drug Discov Today*. 2018;23(1):90–100.
17. Lanthier M, Miller KL, Nardinelli C, Woodcock J. An improved approach to measuring drug innovation finds steady rates of first-in-class pharmaceuticals, 1987-2011. *Health Aff.* 2013;32(8):1433–9.

18. Eder J, Sedrani R, Wiesmann C. The discovery of first-in-class drugs: origins and evolution. *Nat Rev Drug Discov*. 2014;13(8):577–87.
19. Frei E. Curative Cancer Chemotherapy. *Cancer Res*. 1985;45:6523–37.
20. Kaur J, Mohanti BK. Transition from Curative to Palliative Care in Cancer. *Indian J Palliat Care*. 2011;17(1):1–5.
21. Cancer Treatment Centers of America. Difference between Blood Cancers: Leukemia & Lymphoma. Available from: https://www.cancercenter.com/community/blog/2018/05/whats-the-difference-blood-cancers-leukemia-lymphoma-and-multiple-myeloma. Accessed August 26, 2021.
22. European Medicines Agency. Scientific recommendations on classification of advanced therapy medicinal products. Available from: https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/advanced-therapies/advanced-therapy-classification/scientific-recommendations-classification-advanced-therapy-medicinal-products. Accessed November 2, 2021.
23. Europen Medicines Agency. Advanced therapy medicinal products: Overview. Available from: https://www.ema.europa.eu/en/human-regulatory/overview/advanced-therapy-medicinal-products-overview. Accessed October 13, 2021.
24. National Cancer Institute. Targeted Cancer Therapies Fact Sheet. Available from: https://www.cancer.gov/about-cancer/treatment/types/targeted-therapies/targeted-therapies-fact-sheet. Accessed August 27, 2021.