Report

New requirements for AMNOG-dossiers: Investigation of considered evaluations in the context of the benefit assessment by IQWiG and G-BA

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LIST OF ABBREVIATIONS

Abbreviation	Meaning
ACT	Appropriate comparator therapy (*Zweckmäßige Vergleichstherapie*)
AE	Adverse event
AESI	Adverse event of special interest
AMNOG	Act on the Reform of the Market for Medicinal Products (*Arzneimittelmarktneuordungsgesetz*)
CTCAE	Common Terminology Criteria for Adverse Events
G-BA	Federal Joint Committee (*Gemeinsamer Bundesauschuss*)
IQWiG	Institute for Quality and Efficiency in Health Care (*Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen*)
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Effect Model Repeated Measures
PT	Preferred Term
RCT	Randomized Controlled Trial
SAE	Serious Adverse Event
SMQ	Standardized MedDRA Queries
SOC	System Organ Class

EXECUTIVE SUMMARY

Background

Pharmaceutical companies have been required since the introduction of AMNOG in January 2011 to submit benefit assessment dossiers when placing new drugs on the market in Germany. Dossiers must be submitted using specified module templates that impose extensive requirements on the preparation of study data and study evaluations, and thus, create a high level of transparency. Since April 2020, new module templates are mandatory to use, clearly increasing the scope of the benefit dossier. The new requirements introduced a number of additional presentation and preparation requirements, including additional presentation of data cutoffs, additional result presentations (incl. plots) and evaluations of efficacy endpoint and AEs as well as subgroup analyses. Subsequently, the dossier volume increased enormously with a concomitant increase in time and effort required to prepare compliant dossiers. Pharmaceutical companies are critical of the associated additional effort, as it is unclear whether and how the additional evaluations are necessary for the purpose of the benefit assessment. It is noticed, for instance, that many of the new evaluations are largely ignored in the actual decision on additional benefit. If all of those additional evaluations were necessary, it would be expected that they would be considered in the decision-making process.

Research question and methods

The objective was to review the volume of evaluations in dossiers submitted by pharmaceutical companies and to determine the proportion of presented evaluations that were included in or justifiably excluded from IQWiG and/or G-BA in the benefit assessment process. The new requirements in the module templates were reviewed separately. A systematic analysis was conducted to investigate regular dossiers (full assessment versus an appropriate comparator with appropriately planned studies and adequately powered RCTs) compiled using the new module templates and with resolution dating from September 2020 to January 2021. The total number of evaluations in dossiers by pharmaceutical companies was quantified and analyzed presenting separate analyses for efficacy endpoints (incl. sensitivity analyses), AEs (total rate of AEs, AEs by SOC and PT, and AESI), subgroups and result-plots. These evaluations were then added up to give the overall evaluations. The relative proportion of analyses that were included or justifiably excluded by IQWiG and/or G-BA from the individual benefit assessment procedures was averaged to obtain a mean across all 10 procedures. In addition, the influence of data cutoffs on the total number of evaluations was investigated.

Results

A total of 10 procedures were selected to compare dossier requirements. The therapeutic indications comprised oncologic diseases, infectious diseases, diseases of the nervous system and the musculoskeletal system. One to 2 research questions and 1 to 3 data cutoffs were examined in each procedure, with page volumes ranging from 405 to approximately 38,000 pages. The results show that IQWiG and/or G-BA included in the respective benefit assessment report or G-BA resolution/justification, on average, only 16% of the evaluations submitted by the pharmaceutical companies. Moreover, IQWiG and/or G-BA justifiably excluded a further 7% of evaluations by the pharmaceutical companies. Therefore, IQWiG and/or G-BA totally considered, on average, only 23% of the evaluations presented by the pharmaceutical companies in the benefit assessment process (see Figure 1). Subgroup analyses (14% evaluations considered) and result-plots (23% evaluations considered) account for a large part of this huge discrepancy between the number of evaluations presented in dossiers by

pharmaceutical companies and those presented in benefit assessment reports or G-BA resolution/justification. While the proportion of considered evaluations was slightly higher for efficacy endpoints including sensitivity analyses (39% evaluations considered) and AEs (52% evaluations considered), most such evaluations were not included or commented on to a large extent. Additionally, multiple data cutoffs increased the amount of overall evaluations that were not considered by IQWiG and G-BA. For procedures with multiple data cutoffs, the proportion of included or justifiably excluded evaluations was a low 18%, while this was noticeably higher at 29% for procedures with 1 data cutoff.

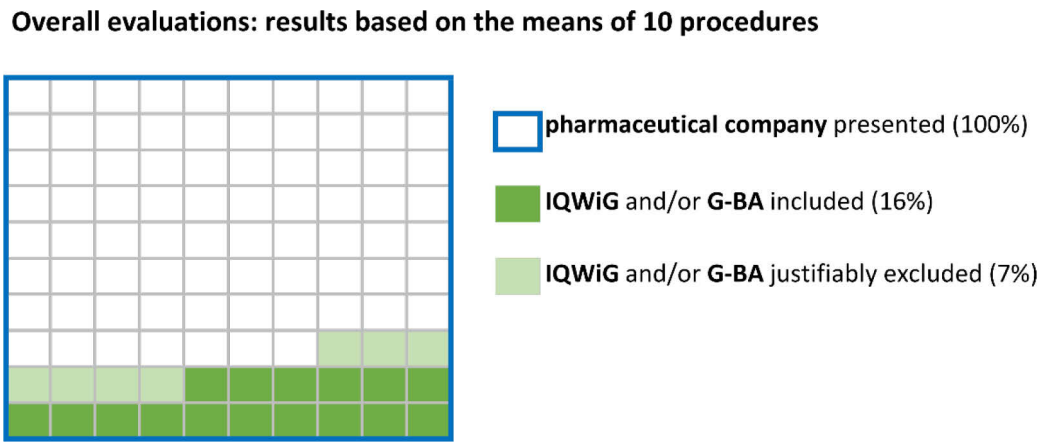

Figure 1: Proportion of evaluations considered by IQWiG and/or G-BA

Note: The cited IQWiG and/or G-BA percentages are means of the relative proportions of the evaluations considered by the institutions.

Conclusion

The investigation shows that the majority of the evaluations in the individual dossiers resulting from the current module templates appear not to be considered by IQWiG and/or G-BA in their benefit assessment process. IQWiG and/or G-BA considered only 23% of the presented evaluations submitted in dossiers by pharmaceutical companies. Based on these results, the scope and level of detail demanded in module templates for benefit dossiers needs to be scrutinized. The pertinence of some parts of the new module template requirements for the benefit assessment is not obvious. In particular, the need of additional data cutoffs, subgroup analyses, and result-plots as well as of efficacy endpoints and AEs is questionable for the benefit assessment. The results of this investigation suggest that large portions of the requirements are unnecessary. Hence, an adjustment of the scope of the current module templates for the additional benefit assessment process seems advisable.

BACKGROUND

The Act on the Reform of the Market for Medicinal Products (Arzneimittelmarktneuordnungsgesetz; AMNOG), which took effect in January 2011 (1), imposes a systematic and formal benefit assessment of medicines with new active ingredients entering the German market. Decisions on additional benefit are the responsibility of the Federal Joint Committee (Gemeinsamer Bundesausschuss; G-BA). Most G-BA assessments are preceded by an evaluation by the Institute for Quality and Efficiency in Health Care (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen; IQWiG). Pharmaceutical companies have to submit a benefit dossier that meets specific formal requirements. These formal requirements are defined in the form of module templates and are incorporated in Annex II of Chapter 5 of the G-BA Rules of Procedure (2). The module templates concrete specifications on the breadth and depth to which the data must be prepared for the benefit dossier and have also been continuously expanded over the years. The latest revision of the module templates came into force on November 6, 2019, and comprised a various number of additional requirements that significantly increased the volume of dossiers, particularly in Module 4 (3). The current module templates, mandatory since April 1, 2020, include requirements for detailed presentation of adverse events (AEs), multiple data cutoffs and additional subgroup analyses. The associated additional workload for pharmaceutical companies is also reflected in the expenses of preparing the benefit dossier.

The submission of dossiers to the G-BA ensures transparency of study data in addition to the additional benefit assessment. However, the data presentation requirements for preparing dossiers should be appropriate. There are doubts about this on behalf of the pharmaceutical industry. It is not clear how these new requirements contribute to the outcome of the benefit assessment (4, 5). For instance, subgroup analyses for certain endpoints would have no impact on the outcome of the benefit assessment in patient groups. Moreover, since May 2020, evaluations presented in the benefit assessment reports receive only the briefest of comments (for example: IQWiG Report - No. 912 (6)). There is an evident disconnect between the extensive demands in the current module templates and the actual inclusion of evaluations in benefit assessment reports or G-BA resolution and justification.

RESEARCH QUESTION

The amount of data presentation required for the preparation of benefit dossiers has increased according to the new module templates that are mandatory since April 1, 2020. Given the background outlined above, the aim of this investigation is to compare the amount of evaluations presented by pharmaceutical companies based on the current module templates (mainly Module 4) with the amount of evaluations considered by IQWiG in the benefit assessment report and/or by the G-BA in the resolution/justification.

These circumstances give rise to the following questions:

- How extensive are the evaluations presented in the dossiers submitted by the pharmaceutical companies?
- What proportion of these evaluations is included in or justifiably excluded from benefit assessments by IQWiG and/or G-BA?
- Do certain parts of the requirements differ from each other in terms of the proportion of evaluations included or justifiably excluded?

METHODS

Selection of the procedures to be analyzed

In order to answer the aforementioned research questions the number of evaluations submitted by pharmaceutical companies in the dossiers and the number of included evaluations by IQWiG-reports and by G-BA resolution/justification were quantified and subsequently compared.

Procedures using the current module template (mandatory since April 1, 2020) were identified for this analysis. Procedures were selected based on the following selection criteria to identify regular dossiers, with an assessment of the submitted analyses by IQWiG or G-BA, for the inclusion in this analysis:

- Procedures that underwent full benefit assessment versus an appropriate comparator therapy (ACT), including non-orphans and orphan drugs generating > €50 million in annual sales. Orphan drugs < €50 million in annual sales were excluded as they do not require the submission of a full dossier versus an ACT.
- Procedures with proper evidence, i.e. involving studies that were considered by IQWiG/G-BA.
- Procedures in which randomized controlled trials (RCTs) were presented.
- Procedures involving sufficiently powered trials, i.e. RCTs with a sample size usually sufficient to enable subgroup analyses.

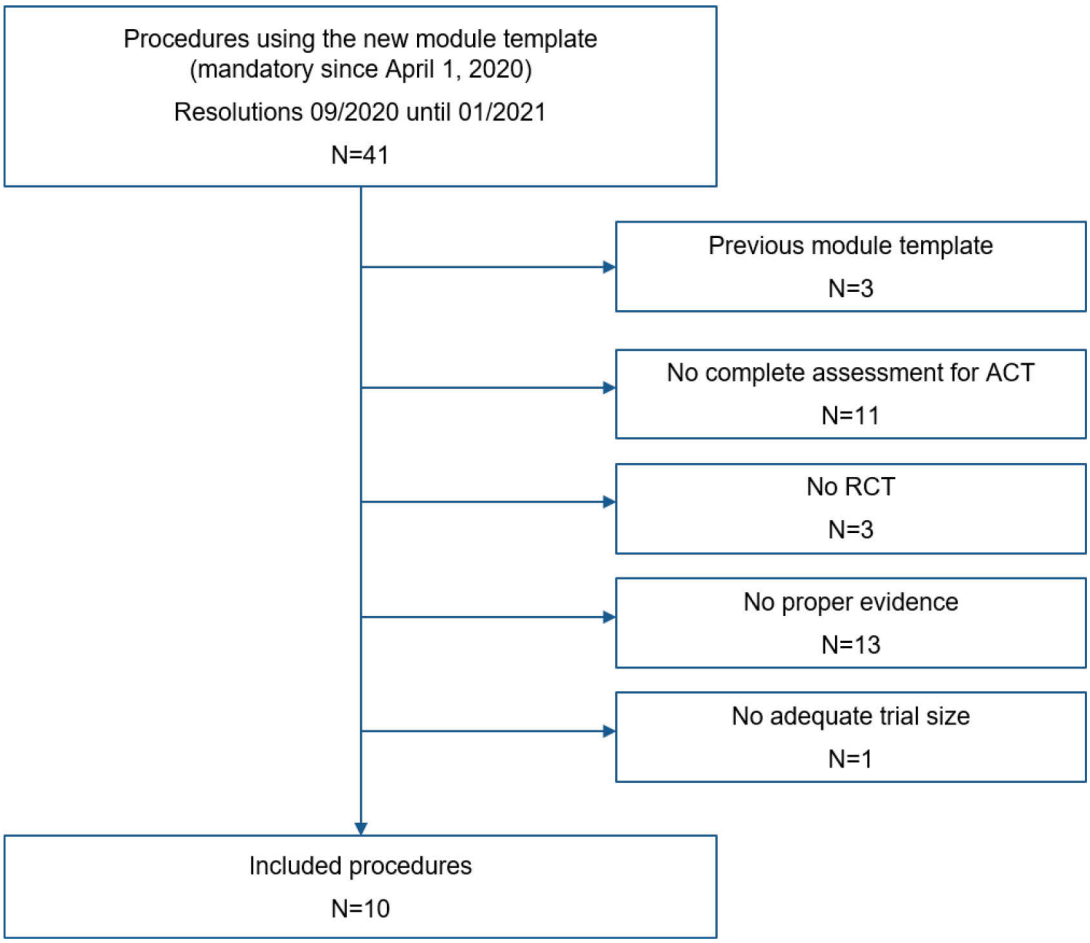

Figure 2: Flow chart - selection of procedures for analysis

ACT: Appropriate comparator therapy; RCT: Randomized controlled trial

Out of 41 identified procedures with a G-BA resolution dating from September 2020 to January 2021, 31 procedures were excluded based on the selection criteria (Figure 2). The 10 procedures included in the analysis are listed in Table 1.

Table 1: Overview of the 10 selected procedures

Serial no.	Procedure		File number	Resolution
1	Apalutamide	Reassessment after the Deadline: Non-metastatic Castration-resistant Prostate Cancer	2020-04-01-D-538	01-Oct-2020
2	Brigatinib	New Therapeutic Indication: NSCLC, ALK+, ALK-inhibitor-naïve patients	2020-05-01-D-542	15-Oct-2020
3	Darolutamide	Non-metastatic Castration Resistant Prostate Cancer	2020-05-01-D-543	15-Oct-2020
4	Encorafenib	New Therapeutic Indication: Metastatic Colorectal Cancer with a BRAF V600E Mutation after Prior Systemic Therapy; in Combination with Cetuximab	2020-07-01-D-551	17-Dec-2020
5	Enzalutamide	Reassessment after the Deadline: Non-metastatic Castration-resistant Prostate Cancer	2020-05-15-D-541	15-Nov-2020
6	Fidaxomicin	New Therapeutic Indication: Clostridioides Difficile Infection, Children and Adolescents	2020-03-15-D-519	03-Sep-2020
7	Ozanimod	Relapsing Remitting Multiple Sclerosis	2020-07-15-D-567	07-Jan-2021
8	Romosozumab	Osteoporosis, Postmenopausal Women	2020-03-15-D-516	03-Sep-2020
9	Talazoparib	Breast Cancer, BRCA1/2-mutation, HER2-	2020-06-01-D-545	20-Nov-2020
10	Trifluridine/ tipiracil	Reassessment after the Deadline: Metastatic Colorectal Cancer	2020-04-01-D-535	01-Oct-2020

The 10 selected procedures are characterized in Table 2. The therapeutic indications comprised oncologic diseases (7 procedures), infectious diseases (1 procedure), diseases of the nervous system (1 procedure) and the musculoskeletal system (1 procedure). Multiple data cutoffs were presented in 5 of the 10 procedures (Apalutamide/2020-04-01-D-538, Darolutamide/2020-05-01-D-543, Romosozumab/2020-03-15-D-516, Talazoparib/2020-06-01-D-545 and Trifluridine/Tipiracil/2020-04-01-D-535). Multiple research questions were described in the Fidaxomicin (2020-03-15-D-519) and Ozanimod (2020-07-15-D-567) procedures. The page volumes in Module 4 of the dossiers range from 405 to 37,919 pages.

Table 2: Characterization of the 10 selected procedures

Serial no.	Procedure	Indication	Trials (trial type)	Number Research questions	Number Data cutoffs	Number of pages Module 4
1	Apalutamide (2020-04-01-D-538)	Oncologic diseases	SPARTAN (RCT)	1	3	1,567
2	Brigatinib (2020-05-01-D-542)	Oncologic diseases	ALTA-1L (RCT)	1	1	405
3	Darolutamide (2020-05-01-D-543)	Oncologic diseases	ARAMIS (RCT)	1	2	37,919
4	Encorafenib (2020-07-01-D-551)	Oncologic diseases	BEACON CRC (RCT)	1	1	1,910
5	Enzalutamide (2020-05-15-D-541)	Oncologic diseases	PROSPER (RCT)	1	1	1,041
6	Fidaxomicin (2020-03-15-D-519)	Infectious diseases	SUNSHINE (RCT)	2	1	1,310
7	Ozanimod (2020-07-15-D-567)	Diseases of the nervous system	Radiance Part B (RCT) Sunbeam (RCT)	2	1	688
8	Romosozumab (2020-03-15-D-516)	Diseases of the musculoskeletal system	ARCH (RCT)	1	2	5,124
9	Talazoparib (2020-06-01-D-545)	Oncologic diseases	EMBRACA (RCT)	1	2	7,519
10	Trifluridine/ tipiracil (2020-04-01-D-535)	Oncologic diseases	RECOURSE (RCT) TERRA (RCT) TALLISUR (non-randomized comparative trial)	1	2	8,702
RCT: Randomized controlled trial						

Evaluation matrix and selection of analysis items

The 10 selected procedures to compare dossier requirements were analyzed using an evaluation matrix in Excel. The evaluation matrix contains various analysis items related to the information in the respective dossier (mainly Module 4), in the IQWiG benefit assessment report and the G-BA resolution and justification.

The following analysis items were included in the evaluation matrix and evaluated in detail:

Evaluation levels

- studies submitted
- populations
- data cutoffs

Evaluations

- efficacy endpoints (incl. sensitivity analyses)
- AEs (total rate of AEs, AEs by system organ class [SOC] and preferred terms [PT], AEs of special interest [AESI])
- subgroups analyses
- result-plots.

For each analysis item, an individual analysis quantified the number of evaluations provided by the pharmaceutical companies and the number of evaluations considered by IQWiG and/or G-BA in their assessments. It is important to distinguish between the following terms:

“Included” means evaluations that were listed as such in the benefit assessment report and/or in the G-BA resolution/justification. “Justifiably excluded" means all evaluations that were excluded or not accepted by IQWiG and/or the G-BA in the aforementioned documents, stating the reasons. Efficacy endpoints and AE analyses require sufficient explanation of patient relevance, validity and significance. An explanation with "not statistically significant" is not sufficient to exclude evaluations on analysis items such as efficacy endpoints or AEs. Evaluations that were either "included" or "justifiably excluded" are collectively deemed as overall “considered" evaluations. The term "evaluations" covers all data presented by the pharmaceutical companies on analysis items including efficacy endpoints (incl. sensitivity analyses), AEs (total rate of AEs, AEs by SOC and PT, and AESI), subgroup analyses and result-plots.

The direction of analysis was from the dossier to the IQWiG-benefit assessment report and G-BA resolution/justification (dossier → benefit assessment report / G-BA). Thus, it was first determined which and how many evaluations the pharmaceutical companies have presented. It was then determined which of these evaluations were taken into consideration by IQWiG and/or G-BA. Evaluations additionally provided in the benefit assessment report or G-BA resolution/justification but not presented by the pharmaceutical companies in the respective procedures were excluded from the analysis. However, all evaluations presented in the appendix or provided as supplementary material were included in the analysis. Due to no publicly available statements of the pharmaceutical companies, any addenda by IQWiG were not included in the evaluation matrix.

The selection of analysis items is based among other things on the current dossier requirements specified by the latest modification of the module templates in Appendix II of Chapter 5 of the G-BA Rules of Procedure (came into force on November 6, 2019). This includes in the first instance the presented evaluation levels of individual trials, any separately presented populations and data cutoffs. Due to the new data cutoff requirements, these are extracted and assessed separately in this analysis. This is done because of the requirement that evaluations must be performed and presented completely for all of the listed data cutoffs even if a data cutoff was originally intended only for evaluation of specific individual endpoints. Granted, "data cutoffs with no relevant information gain" or "data cutoffs in close temporal proximity to another data cutoff" may be omitted. The problem cited by the pharmaceutical industry is that the criteria for omitting these analyses are not clearly specified. Resultant concerns about potential formal incompleteness can prompt pharmaceutical companies to continue submitting evaluations on multiple data cutoffs, with all the immense additional effort involved (5, 7).

Other analysis items include the individual evaluations on efficacy endpoints, AEs, subgroup analyses and result-plots.

Efficacy endpoint and AE evaluations are core evaluations required for submission in benefit assessment dossiers. AE analysis includes the new requirements for AE presentation at SOC and PT level and newly proposed thresholds. AE evaluations by organ system and single events according to Medical Dictionary for Regulatory Activities (MedDRA) are required for all 4 categories of AEs (total rate of AEs, total rate of serious AEs [SAEs], discontinuations due to AEs, total rate of AEs classified by severity). In addition, AESI evaluations are also required for this analysis item. The exact number of additional endpoints varies depending on the type of disease, severity of disease, trial size and, not least, the side effect profile of the active substance. For instance, the large number of additional AE endpoints is problematic in oncological trials, as multiple data cutoffs and large numbers of subgroups often lead to a multiplicity of AE evaluations (5, 7). The new module templates also impose additional requirements for evaluations of subgroup analyses. In addition to evaluations of the socially relevant characteristics of gender, age, disease severity or stage, and center or country effects, pharmaceutical companies also need to present results of subgroup analyses for all endpoints that are specified in the trial protocol (5, 7). Other requirements of the new module templates include the presentation of result-plots. Survival analyses are required for instance if observation times differ between treatment groups, with Kaplan-Meier curves to be presented in each case. There is also a requirement to present graphical representations for all patient-reported outcomes collected using scales and meta-analyses (5, 7).

Data analysis methodology

Two reviewers independently performed the analysis of the selected 10 procedures focusing on the defined analysis items in the evaluation matrix as described above. The results were then consolidated. Any discrepancies were discussed. For the quantitative calculation, all evaluations concerning the analysis items efficacy endpoints (incl. sensitivity analyses), AEs (total rate of AEs, AEs by SOC and PT, and AESIs), subgroup analyses and result-plots were first counted separately and then added up for the overall evaluations:

$$\#Overall\ evaluations = \#Efficacy\ endpoints\ + \#AE + \#Subgroup\ analyses + \#Plots$$

The reviewers only counted evaluations of trials and populations that were also taken into consideration by the G-BA. Multiple counting was performed for evaluations for which multiple trials, populations or data cutoffs were presented or considered in the benefit assessment report and G-BA resolution/justification. For example, evaluations concerning one endpoint were counted multiple times if it was presented in different data cutoffs.

For the “data cutoffs” analysis item, the simple number of data cutoffs presented by the pharmaceutical company was not included in the total for the overall evaluation. However, evaluations of data cutoffs can affect the overall evaluation via the multiple counting of additional analysis items, as described. This influence of data cutoffs on the number of submitted evaluations is presented separately in the results section.

In addition, the following evaluations or data were not included in the overall evaluation: Information gathering, research question (ACT) and risk of bias. The results of this analysis for the submitted evaluations of the 10 procedures were listed separately for the pharmaceutical company, IQWiG and G-BA. The results were also subdivided according to which of the pharmaceutical company’s evaluations were included by IQWiG and G-BA and which were justifiably excluded. This resulted in the proportion of the pharmaceutical company’s evaluations that were considered by IQWiG and/or G-BA. Further details of the evaluations on the analysis items are provided in the focus boxes in the corresponding subsections of the results section. The relative proportion of analyses that were included or justifiably excluded from the individual benefit assessment procedures was averaged to obtain a mean across all 10 procedures.

RESULTS

Overall evaluations

For the 10 procedures analyzed, the joint presentation of IQWiG and/or G-BA results included, on average, 16% of the evaluations presented by the pharmaceutical companies in the respective benefit assessment report or G-BA resolution/justification. IQWiG and/or G-BA justifiably excluded a further 7% of evaluations presented by the pharmaceutical companies. Thus, IQWiG and/or G-BA considered, on average, 23% of the evaluations presented by the pharmaceutical companies (see Figure 3).

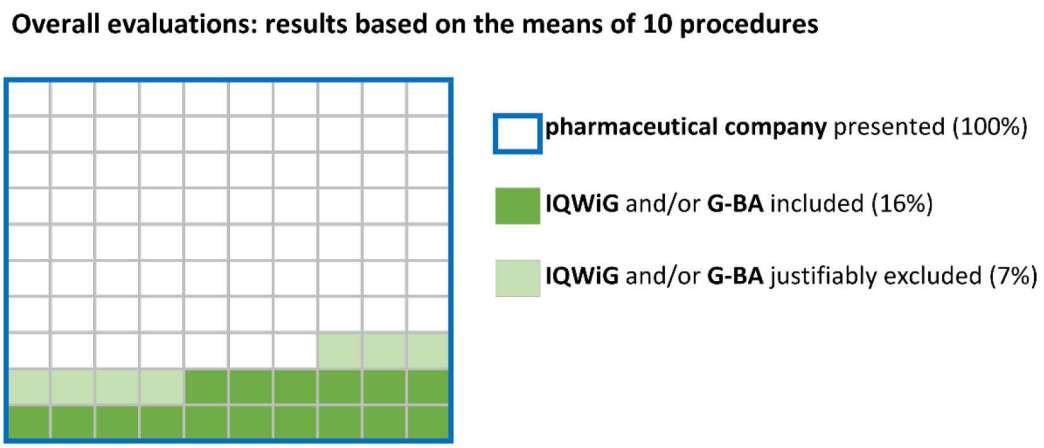

Figure 3: Proportion of evaluations considered by IQWiG and/or G-BA

Note: The cited IQWiG and/or G-BA percentages are means of the relative proportions of the evaluations considered by the institutions.

In the 10 procedures analyzed, the mean number of evaluations presented by the pharmaceutical companies (efficacy endpoints incl. sensitivity analyses, AEs, subgroup analyses and result-plots) was 3,935 analyses. The minimum was 571 evaluations in the procedure Fidaxomicin (2020-03-15-D-519) and the maximum was 16,169 evaluations in the procedure Trifluridine/Tipiracil (2020-04-01-D-535) (see Table 3 to Table 12).

In the case of Trifluridine/Tipiracil (2020-04-01-D-535), two RCTs were available for meta-analysis. In addition, another data cutoff was available for one of the two RCTs which was fully presented. Since this is an oncological procedure, where durations of observation differ between treatment groups, survival time analyses had to be performed across endpoints and Kaplan-Meier curves had to be presented.

The lowest percentage of neither included nor justifiably excluded evaluations was in the procedure Trifluridine/Tipiracil (2020-04-01-D-535; Table 12), with only 6% of the evaluations being considered by IQWiG and/or G-BA. The highest percentage of considered evaluations was identified for the procedure Darolutamide (2020-05-01-D-543; Table 5), where 39% of the evaluations presented by the pharmaceutical company were considered by IQWiG and/or G-BA. Out of 6,928 evaluations presented by the pharmaceutical company in this procedure, IQWiG and/or G-BA included only 304 evaluations (4%) and 2,434 evaluations (35%) were justifiably excluded. The high percentage of justifiably excluded evaluations can be explained by the fact

that a complete data cutoff submitted by the pharmaceutical company on the basis of the module templates was excluded, resulting in all the analyses of this data cutoff being deemed justifiably excluded.

Data cutoffs

Module template requirements (7):

4.3.1.3.1 <Endpoint xxx> – RCT

(…) Evaluations of the data cutoffs in section 4.3.1.2.1 are to be conducted and presented in full, i.e. for all of the relevant endpoints investigated. This applies even if a data cutoff was originally intended only for the evaluation of selected endpoints. There is no need to report the results of individual endpoints of a data cutoff or of a total data cutoff if it would be unlikely to provide useful additional information versus another data cutoff (e.g. if follow-up on an endpoint was virtually complete at the previous data cutoff or if one data cutoff follows another in close succession). (…)

Focus of analysis:

Which data cutoffs were presented in the dossier and were included in or justifiably excluded from the benefit assessment report or G-BA resolution/justification? Data cutoffs presented by the pharmaceutical company in the appendix were also counted (including data cutoffs provided as supplementary material).

A data cutoff is deemed included if it is used in the benefit assessment report or G-BA resolution/justification. Presentation of the data cutoffs in the appendix is sufficient for this purpose.

A data cutoff is deemed justifiably excluded if there is a sufficient, explicit explanation for the exclusion.

For all data cutoffs listed, evaluations must be performed and presented in their entirety, even if a data cutoff was originally intended only for the evaluation of individual endpoints. This can lead to a multiplication of the analyses to be presented.

The analysis revealed that 5 of the 10 procedures presented multiple data cutoffs for at least one trial (Apalutamide/2020-04-01-D-538, Darolutamide/2020-05-01-D-543, Romosozumab/2020-03-15-D-516, Talazoparib/2020-06-01-D-545, and Trifluridine/Tipiracil/2020-04-01-D-535). IQWiG and/or G-BA included only one data cutoff in each case. Justifiable exclusion of a data cutoff only took place in the procedure Darolutamide (2020-05-01-D-543).

In the procedures with only 1 data cutoff (per trial) presented, the pharmaceutical companies submitted an average of 1,393 evaluations. In the procedures with multiple data cutoffs (for at least one trial) presented, the pharmaceutical companies submitted an average of 6,477 evaluations. Thus, the number of submitted evaluations with multiple data cutoffs was 4 to 5 times higher than with just 1 data cutoff. IQWiG and/or G-BA considered 29% of the evaluations in the procedures comprising 1 data cutoff and only considered 18% of the evaluations in the procedures comprising multiple data cutoffs (see Figure 4).

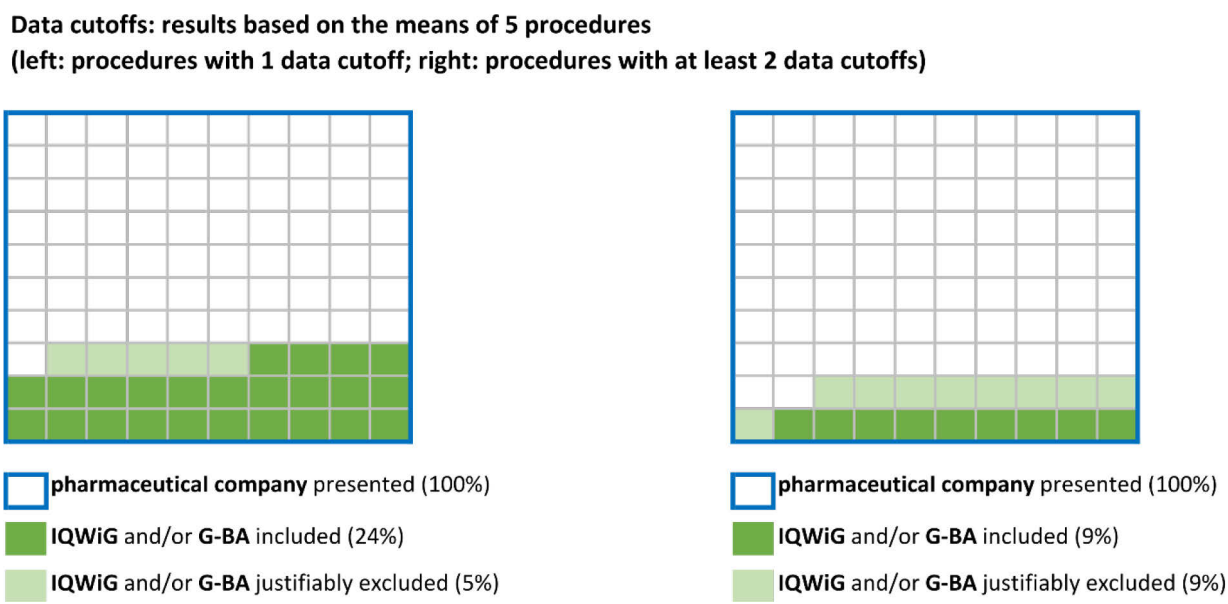

Figure 4: Proportion of evaluations considered by IQWiG and/or G-BA, broken down by number of data cutoffs

Note: The cited IQWiG and/or G-BA percentages are means of the relative proportions of the evaluations considered by the institutions.

The extent to which multiple data cutoffs can increase the number of overall evaluations can be seen for instance in the procedure Trifluridine/Tipiracil (2020-04-01-D-535; Table 12). In that procedure, 2 data cutoffs were presented for the RECOURSE trial, of which only one was considered in IQWiG's benefit assessment report and in the G-BA resolution/justification. The pharmaceutical company presented in total 16,169 evaluations in the procedure. Only 815 evaluations (5%) were included in IQWiG's benefit assessment report and the G-BA resolution/justification and 78 evaluations (1%) were justifiably excluded.

Efficacy endpoints (incl. sensitivity analyses)

Module template requirements (7):

4.2.5.2 Comparison of the results of the individual studies

The results of the individual studies are reported separately in the first instance for each included study in the appropriate subsections of sections 4.3.1 and 4.3.2. The information presented should include the characteristics of the study populations and the results for all the patient-relevant endpoints reported in the included studies (health improvement, reduction in disease duration, extension of survival, reduction of side effects, improvement in quality of life). Reporting requirements are described in the subsections.

4.2.5.4 Sensitivity analyses

Sensitivity analyses should be conducted to methodological factors to estimate the robustness of the results. Methodological factors are based on the decisions made during information procurement and assessment, e.g. determining cutoff values for survey times or choosing the effect size. The classification of risk of bias of results into the categories "high" and "low" is particularly important for sensitivity analyses.

The result of the sensitivity analyses can influence the estimation of the significance of the proofs.

Focus of analysis:

Which efficacy endpoints (incl. sensitivity analyses) were presented in the dossier and were included in or justifiably excluded from the benefit assessment report or G-BA resolution/justification? Efficacy endpoints presented by the pharmaceutical company in the appendix were also counted (including efficacy endpoints provided as supplementary material).

An efficacy endpoint is deemed included if it is used in the benefit assessment report or G-BA resolution/justification. Presentation of the endpoints in the appendix is sufficient for this purpose.

An efficacy endpoint is deemed justifiably excluded if there is a sufficient explanation based on patient relevance, validity and significance. An explanation with "not statistically significant" is not sufficient to exclude data.

The module template requires pharmaceutical companies to present results for all patient-relevant endpoints reported in the included trials. In order to meet the high requirements, pharmaceutical companies commonly also present numerous sensitivity analyses.

In the 10 procedures analyzed, the average number of efficacy endpoints (incl. sensitivity analyses) was 98. The number of efficacy endpoints presented ranged from 6 in the procedure Enzalutamide (2020-05-15-D-541) to 203 in the procedure Encorafenib (2020-07-01-D-551) (see Table 3 to Table 12).

IQWiG and/or G-BA included, on average, 22% of the efficacy endpoints presented and justifiably excluded another 17%. On average, only 39% of the efficacy endpoints presented by the pharmaceutical companies (incl. sensitivity analyses) were considered in the assessment (see Figure 5).

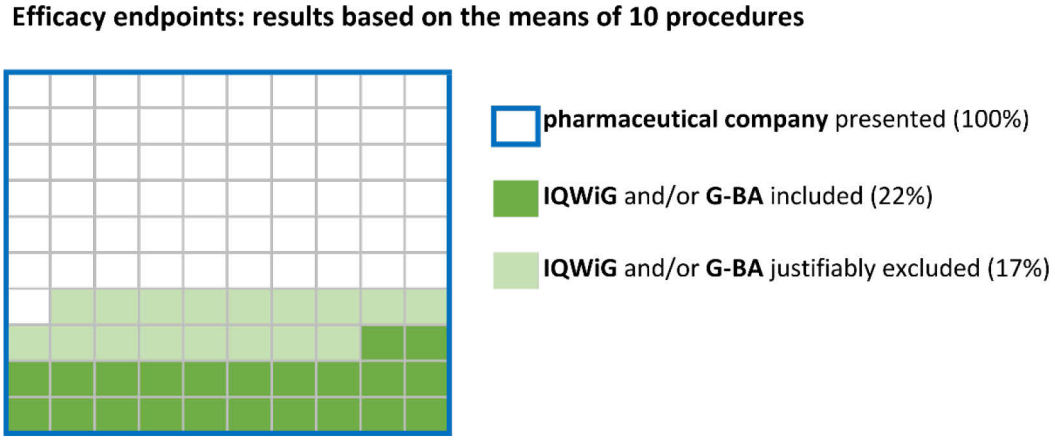

Figure 5: Proportion of efficacy endpoints (incl. sensitivity analyses) considered by IQWiG and/or G-BA

Note: The cited IQWiG and/or G-BA percentages are the means of the relative proportions of efficacy endpoints considered by the institutions.

The percentage of efficacy endpoints considered in benefit assessment ranged from 10% in the procedure Apalutamide (2020-04-01-D-538; Table 3) to 70% in the procedure Darolutamide (2020-05-01-D-543;) Table 5). Any differences between IQWiG and G-BA regarding which efficacy endpoints were included or justifiably excluded tended to be minor (see Figure 10).

Adverse events (AEs)

Module template requirements (7):

4.3.1.3.1 <Endpoint xxx> – RCT

(…) Report the following evaluations of adverse events (AEs):

1. Total rate of AEs

2. Total rate of serious AEs (SAEs)

3. Total rate of discontinuation due to AEs,

4. Total rate of AEs differentiated by severity, if this information was generated in the relevant study/studies (e.g., based on CTCAE and/or other established/validated indication-specific classification) including differentiation between severe and non-severe AEs,

5. In addition to stating the total rate for the categories indicated in 1, 2 and 4 (AEs, not further differentiated; SAEs, AEs differentiated by severity), also arrange the AEs by organ systems and single events (System Organ Classes [SOCs] and Preferred Terms [PTs] by MedDRA) using the following criteria:

- AE (any severity): events occurring in at least 10% of patients in one study arm

- Severe AEs (e.g. CTCAE grade ≥ 3) and SAEs: events occurring in at least 5% of patients in one study arm

- in addition, for all events of any severity: events occurring in at least 10 patients AND in at least 1% of patients in any study arm.

6. Report a priori defined AEs of special interest (AESI) and predefined SOC-overreaching AE evaluations (e.g. as Standardized MedDRA Queries, SMQs) of any event rate, sorted by severity (reported as total rate and differentiated by severity, non-severe, severe, serious). (…)

Focus of analysis:

Which AEs (total rate of AEs, AEs by SOC and PT, and AESIs) were presented in the dossier and were included in or justifiably excluded from the benefit assessment report or G-BA resolution/justification? AEs presented by the pharmaceutical company in the appendix were also counted (including AEs provided as supplementary material).

An AE is deemed included if it is used in the benefit assessment report or G-BA resolution/justification. Presentation of the AE in the appendix is sufficient for this purpose.

An AE is deemed justifiably excluded if there is sufficient explanation based on patient relevance, validity and significance. An explanation with "not statistically significant" is not sufficient to exclude data.

Adverse events (AEs) are subdivided into total rate, AEs by SOC and PT and AESI (broken down in each case by AE, SAE, discontinuation due to AEs and AEs differentiated by severity). Due to the requirements of the module template, the number of AEs to be presented greatly depends on the disease involved, the trial size and the number of prespecified AESIs.

The average number of AEs presented in the 10 analyzed procedures was 593 AEs. The fewest AEs were presented in the procedure Fidaxomicin (2020-03-15-D-519) (111 AEs). The largest number of AEs was presented in the procedure Romosozumab (2020-03-15-D-516) (1,528 AEs) (see Table 3 to Table 12).

IQWiG and/or G-BA included, on average, 40% of the AEs presented and justifiably excluded another 12%. On average, 52% of the AEs presented by the pharmaceutical companies were considered in the assessment (see Figure 6).

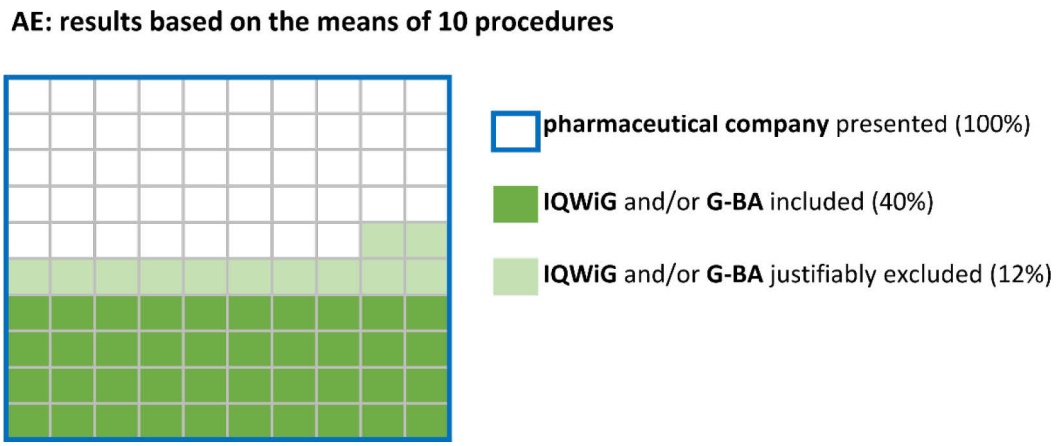

Figure 6: Proportion of AEs considered by IQWiG and/or G-BA

Note: The cited IQWiG and/or G-BA percentages are the means of the relative proportions of AEs considered by the institutions.

The proportion of considered evaluations is higher for AEs than for efficacy endpoints (incl. sensitivity analyses) (39% vs. 52%). The higher percentage for AEs results from the fact that the evaluations by SOC and PT associated with this analysis item are usually presented in the appendix of an IQWiG benefit assessment report and are deemed as included evaluations based on this criterion. Analysis of the further handling of the AEs listed in the appendices was not possible within the scope of the present investigation.

Except for a few AEs, the G-BA resolution/justification did not clearly indicate which of the presented AEs were actually considered in the decision-making process. On average, 4% of AEs were included and 0% of AEs were justifiably excluded (see Figure 11).

Subgroup analyses

Module template requirements (7):

4.2.5.5 Subgroup characteristics and other effect modifiers

(…) If meaningful, the following factors should be considered in terms of possible effect modification:

– Gender

– Age

– Severity or stage of the disease

– Center and country effects

If clues for additional, possible effect modifiers result from the available information, these can also be justified and included. The results of subgroup analyses for patient-relevant endpoints planned a priori in studies and stipulated in the study protocol must always be represented (for more additional reporting criteria, see section 4.3.1.3.2). (…)

Focus of analysis:

Which subgroup analyses were presented in the dossier and were included in or justifiably excluded from the benefit assessment report or G-BA decision/justification? Subgroup analyses presented by the pharmaceutical company in the appendix were also counted (including subgroup analyses provided as supplementary material).

A subgroup analysis is deemed included (or justifiably excluded) if both the associated subgroup and endpoint were included (or justifiably excluded). The subgroup analysis does not have to be explicitly mentioned. Presentation of the subgroup analyses in the appendix is sufficient for this purpose.

A subgroup analysis is deemed justifiably excluded if the associated subgroup was included and only the endpoint was justifiably excluded.

The number of subgroup analyses greatly depends on the number of prespecified subgroups in a trial. According to the module template, prespecified subgroups are always to be presented for patient-relevant endpoints, whereas in the present trials this mostly refers only to the primary endpoint.

The number of subgroup characteristics presented in the 10 analyzed procedures ranged from 4 to 19. The G-BA considered 0 to 3 subgroup characteristics in each case (depending on benefit assessment procedure: age, gender, and Severity of the disease); no subgroups were justifiably excluded in any of the procedures.

The average number of subgroup analyses in the 10 analyzed procedures was 1,718 subgroup analyses. The number of subgroup analyses ranged from 412 subgroup analyses in the procedure Fidaxomicin (2020-03-15-D-519) to 4,687 subgroup analyses in the procedure Encorafenib Trifluridine/Tipiracil (2020-04-01-D-535) (see Table 3 to Table 12).

IQWiG and/or G-BA included, on average, 12% of the subgroup analyses presented and justifiably excluded another 2%. On average, only 14% of the subgroup analyses presented by the pharmaceutical companies were considered in the benefit assessment (see Figure 7).

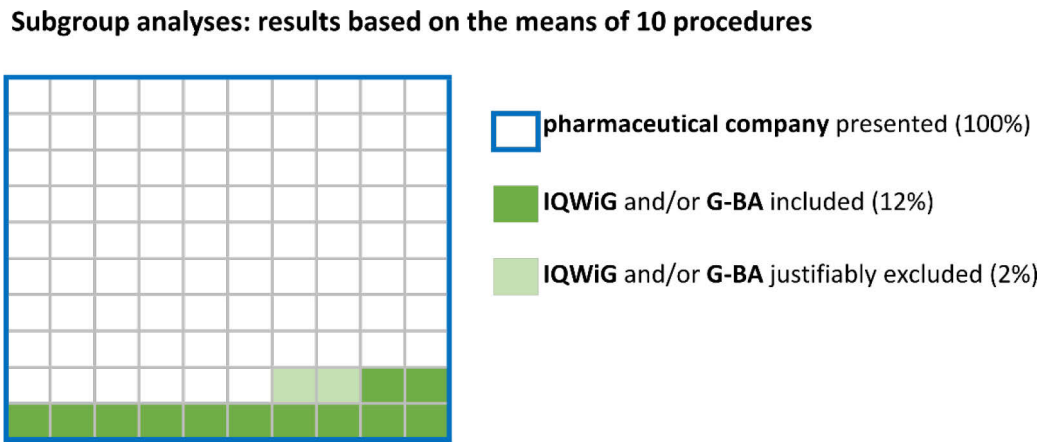

Figure 7: Proportion of subgroup analyses considered by IQWiG and/or G-BA

Note: The cited IQWiG and/or G-BA percentages are the means of the relative proportions of subgroup analyses considered by the institutions.

Except for a few subgroup analyses, the G-BA resolution/justification did not clearly indicate which of the presented subgroup analyses were actually considered in the decision-making process. On average, 2% of subgroup analyses were included and 0% of subgroup analyses were justifiably excluded (see Figure 12).

In the procedure Encorafenib (2020-07-01-D-551; Table 6), not a single one of the 1,871 presented subgroup analyses was considered by IQWiG and/or G-BA. The highest proportion of subgroup analyses considered was seen in the procedure Brigatinib (2020-05-01-D-542; Table 4), where 177 of 632 (28%) presented subgroup analyses were considered in the assessment.

Result-plots

Module template requirements (7):

4.3.1.3.1 <Endpoint xxx> – RCT

(…) For survival analyses, present the Kaplan-Meier curve including specification of patients at risk over time (at different points in time). Provide a separate Kaplan-Meier curve for each endpoint for which any such analysis is performed.

If you are using scale-based patient-reported endpoints (e.g. on health-related quality of life or symptoms), always indicate the values collected during the study, including in a graphical representation and include an evaluation that fully addresses all the information generated during the study (e.g. symptom burden over time, estimated using MMRM analysis [if appropriate in regard to the body of evidence]). (…)

(…) If the available studies are suitable for a meta-analysis, the meta-analyses should be presented as a forest plot. The representation should contain sufficient information to assess heterogeneity in the results between the studies in the form of appropriate statistical measures (see section 4.2.5.3). (…)

Focus of analysis:

Which result-plots (Kaplan-Meier plots, process graphs for continuous analyses, forest plots for meta-analyses) were presented in the dossier and were included in or justifiably excluded from the benefit assessment report or G-BA resolution/justification? Result-plots presented in the appendix were also counted, or are deemed to be included (including result-plots provided as supplementary material).

A result-plot is deemed included if it is used in the benefit assessment report or G-BA resolution/justification. Presentation of the result-plots in the appendix is sufficient for this purpose.

A result-plot is deemed justifiably excluded if the associated endpoint has also been justifiably excluded.

For survival analyses, continuous patient-reported endpoints and meta-analyses, graphical representations are mandatory according to the module templates. Hence, the number of result-plots to be presented greatly depends on the type of endpoints and the feasibility of a meta-analysis.

The average number of result-plots in the 10 analyzed procedures was 1,526. The number of result-plots ranged from 16 results-plots in the procedure Fidaxomicin (2020-03-15-D-519) to 10,521 in the procedure Trifluridine/Tipiracil (2020-04-01-D-535) (see Table 3 to Table 12).

IQWiG and/or G-BA included, on average, 7% of the result-plots presented and justifiably excluded another 16%. On average, 23% of the result-plots presented by the pharmaceutical companies were considered in the benefit assessment (see Figure 8).

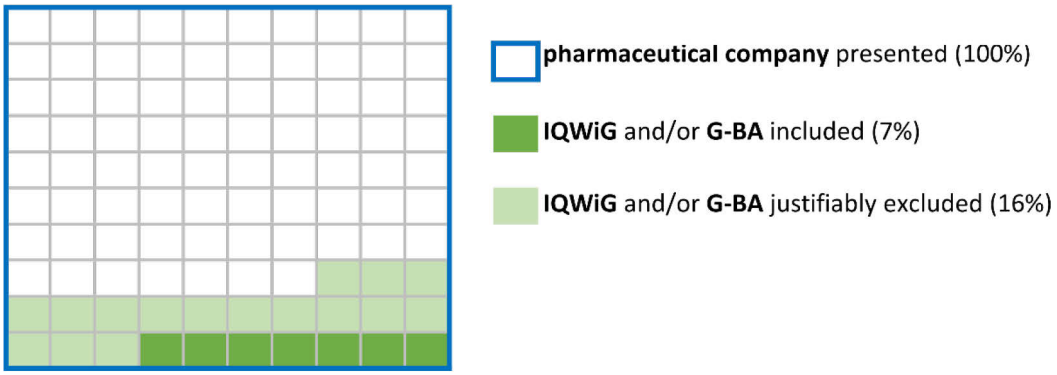

Figure 8: Proportion of result-plots considered by IQWiG and/or G-BA

Note: The cited IQWiG and/or G-BA percentages are means of the relative proportions of the results plots considered by the institutions.

The G-BA resolution/justification generally did not clearly indicate to which extent the result-plots were considered in the decision-making process (see Figure 13).

DISCUSSION

The analyses of the 10 selected procedures clearly indicate that IQWiG and/or G-BA ignore many of the evaluations in the dossiers based on the current requirements of the module templates.

IQWiG and/or G-BA considered, on average, only 23% of the evaluations presented by the pharmaceutical companies. Particularly, with regard to subgroup analyses and result-plots, a large discrepancy is evident between the evaluations presented by the pharmaceutical companies and the evaluations considered by IQWiG and/or G BA. On average, only 14% of subgroup analyses and 23% of result-plots presented by the pharmaceutical companies were considered in the assessment. The percentage of presented evaluations considered by IQWiG and/or G-BA was slightly higher for efficacy endpoints (incl. sensitivity analyses) and AEs (39% and 52%, respectively); however, the evaluations were not included or commented on to a high extent. Thus, there is clear potential modifying the requirements of the module template to avoid unnecessary amounts of data that have to be produced and commented on, which finally have no impact on the benefit assessment report and the resolution.

The pharmaceutical companies are also critical with the new requirements for data cutoffs. In particular, evaluations must be performed and presented completely for all of the listed data cutoffs even if a data cutoff was originally intended only for evaluation of specific individual endpoints. Each additional data cutoff that has to be submitted by a pharmaceutical company multiplies the analyses to be presented and the expenses of preparing the benefit dossier. The German Association of Researching Pharmaceutical Companies (vfa) reported that the average cost of a dossier were recently around €1,000,000, which is 250 times higher than estimated when the benefit assessment was first introduced. In addition, since the last update of the module templates, the number of pages has increased four- to five-fold from approximately 750 to approximately 3,500 pages (8). In individual cases, the number of pages even reach 20,000 to 40,000 pages in order to meet the requirements of the G BA (for example: Darolutamide/2020-05-01-D-543).

The analysis of data cutoffs revealed that in 5 procedures with multiple data cutoff presentation (for at least one trial) only 18% of the evaluations presented by the pharmaceutical companies were considered in the IQWiG and/or G-BA assessment. In comparison, for the 5 procedures with only 1 data cutoff, 29% of the evaluations were considered by IQWiG and/or G-BA. The procedure of Darolutamide (2020-05-01-D-543) is a good example to elucidate the problem involved in having to perform and present evaluations completely for all listed data cutoffs. The pharmaceutical company presented 2 data cutoffs for the ARAMIS trial. Only one of the two data cutoffs was considered in the benefit assessment report and G-BA resolution/justifiaction. A detailed justification to exclude the other data cutoff was available. Nonetheless, the pharmaceutical company presented 2 data cutoffs due to the module template requirements. Non-compliance to these requirements would have risked a charge of formal incompleteness. The pharmaceutical company generated in total 6,928 evaluations for the procedure Darolutamide. Only 304 evaluations (4%) were included in the benefit assessment report and the G-BA resolution/justification and 2,434 evaluations (35%) were justifiably excluded. Thus, the new data cutoff requirements particularly increase the numbers of evaluations that are not considered in the benefit assessment process.

The present investigation has several limitations. It remains unclear whether additional evaluations beyond those considered in the procedures were considered in the assessment and whether these were only insufficiently commented on by IQWiG and G-BA. If so, the proportion of evaluations deemed as “considered” may be an underestimation of the evaluations actually considered by IQWiG and G-BA. However, no indications of a lack of diligence in commenting have been found in benefit assessments in practice so far. Another limitation of this investigation involved the fact that a more in-depth analysis of the evaluations intended for actual consideration (e.g. AEs listed in the appendices of IQWiG assessments) was not possible. Since the mere listing of the evaluations in the assessment reports was counted as inclusion, actual consideration may have been overestimated.

Other limitations of this analysis involved sample size and evaluation methods. In total, 10 procedures were considered and evaluated for the research questions. These procedures comprised benefit assessment dossiers submitted to the G-BA between March 2020 and August 2020, hence, with resolution dating from September 2020 to January 2021. Any other procedures with a later starting date were not included in the analysis. The evaluation methods also have limitations with regard to the lack of consideration of possible IQWiG addenda. Since statements by pharmaceutical companies are not accessible to the public, they could not be included properly in the analysis. The analysis is also limited by the fact that, with a few exceptions, it was not apparent which of the presented AEs and subgroup analyses were actually included in G-BA resolution. Likewise, it was not apparent whether or to what extent the G-BA considered result-plots in its resolution.

In addition, it was recognized during the analysis that in all 10 analyzed procedures the so far usual section "Comments on the pharmaceutical company's dossier" was absent in the respective IQWiG assessments. As a result, a number of evaluations lacked transparent justifications for the handling of the submitted data. The pharmaceutical companies may therefore be missing valuable information that would be essential for preparing a statement or planning a subsequent dossier. Nevertheless, it would have been expected that the extensive requirements of the current module templates would at least have been considered and commented on in the benefit assessment reports and G-BA resolutions/justifications.

CONCLUSIONS

Based on the results, the scope and level of detail demanded in module templates for benefit dossiers needs to be scrutinized. The results of this analysis questioned the merit of the extended requirements for benefit assessment purposes particularly with respect to data cutoffs, subgroup analyses and result-plots as well as for efficacy endpoints and AEs. The results of this investigation suggest that large portions of the requirements are unnecessary. Hence, an adjustment of the scope of the current module templates for the additional benefit assessment process seems advisable.

REFERENCES

1. Bundestag. Gesetz zur Stärkung der Arzneimittelversorgung in der gesetzlichen Krankenversicherung (Arzneimittelmarktneuordnungsgesetz – AMNOG); 22. Dezember. 2010. Verfügbar unter: https://www.bgbl.de/xaver/bgbl/start.xav?start=%2F%2F*[%40attr_id%3D%27bgbl110s2262.pdf%27]#__bgbl__%2F%2F*%5B%40attr_id%3D%27bgbl110s2262.pdf%27%5D__1621927533334. [Zugriff am: 25.05.2021]
2. Gemeinsamer Bundesausschuss. Verfahrensordnung des Gemeinsamen Bundesausschusses; 03. Juni. 2021. Verfügbar unter: https://www.g-ba.de/downloads/62-492-2504/VerfO_2017-11-17_iK-2021-06-03.pdf. [Zugriff am: 29.06.2021]
3. Gemeinsamer Bundesausschuss. Bekanntmachung eines Beschlusses des Gemeinsamen Bundesausschusses über eine Änderung der Verfahrensordnung (VerfO): Änderung der Anlage II zum 5. Kapitel vom 16. März 2018; 05. November. 2019. Verfügbar unter: https://www.bundesanzeiger.de/pub/publication/dTK8jp2bmaD6qJFBvci/content/dTK8jp2bmaD6qJFBvci/BAnz%20AT%2005.11.2019%20B2.pdf?inline. [Zugriff am: 25.05.2021]
4. Verband Forschender Arzneimittelhersteller. Stellungnahme zur Änderung der G-BA Verfahrensordnung vom 16. März 2018 – Modulvorlagen; 02. Mai. 2018. [Zugriff am: 06.04.2021]
5. Verband Forschender Arzneimittelhersteller. Stellungnahme zum G-BA Workshop zur Begrenzung der Dossiervorlagen; 26. November. 2018. [Zugriff am: 06.04.2021]
6. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG). IQWiG-Berichte – Nr. 912: Ramucirumab (NSCLC, Kombination mit Erlotinib) – Nutzenbewertung gemäß §35a SGB V; Stand: 13.05. 2020. Verfügbar unter: https://www.g-ba.de/downloads/92-975-3516/2020-02-15_Nutzenbewertung-IQWiG_Ramucirumab_D-515.pdf. [Zugriff am: 09.06.2021]
7. Gemeinsamer Bundesausschuss. Modul 4 – Medizinischer Nutzen und medizinischer Zusatznutzen, Patientengruppen mit therapeutisch bedeutsamem Zusatznutzen; Stand: 21. Februar. 2019. Verfügbar unter: https://www.g-ba.de/downloads/17-98-4825/2019-02-21_Anl2_6_Modul4.pdf. [Zugriff am: 28.05.2021]
8. Verband Forschender Arzneimittelhersteller. 10 Jahre AMNOG – Sicht der forschenden Pharmaunternehmen; 19. März. 2021. Verfügbar unter: https://www.g-ba.de/downloads/17-98-5090/G-BA_10-Jahre-AMNOG_Vortragsfolien_VA-19-03-2021.pdf. [Zugriff am: 06.04.2021]

APPENDIX

Figures

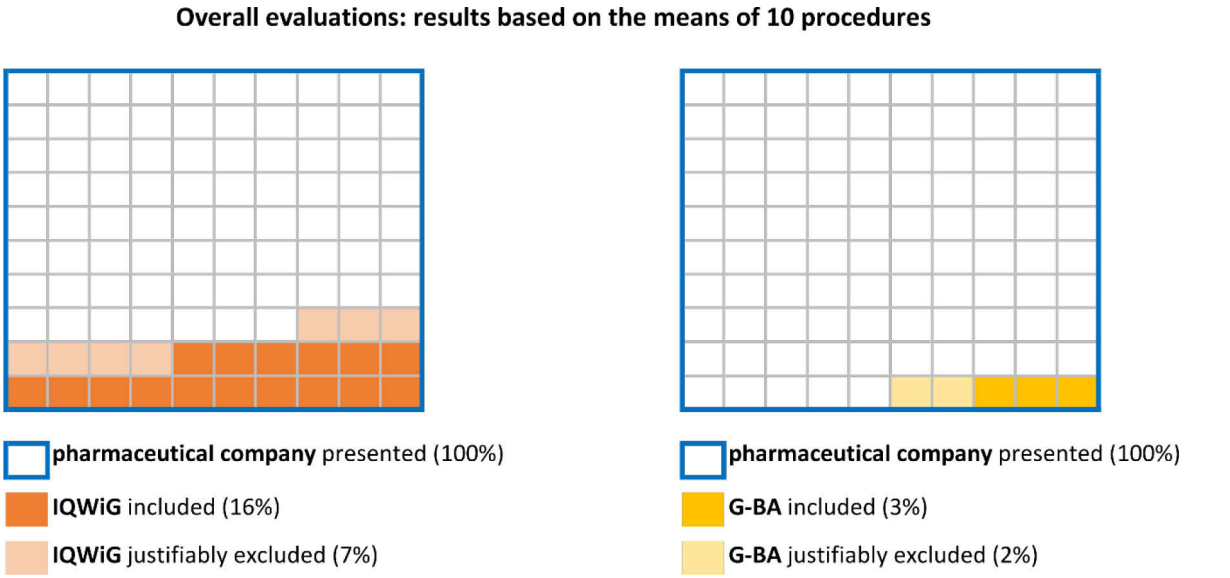

Figure 9: Proportion of evaluations considered by IQWiG and G-BA

Note: The cited IQWiG and G-BA percentages are means of the relative proportions of the evaluations considered by the institutions.

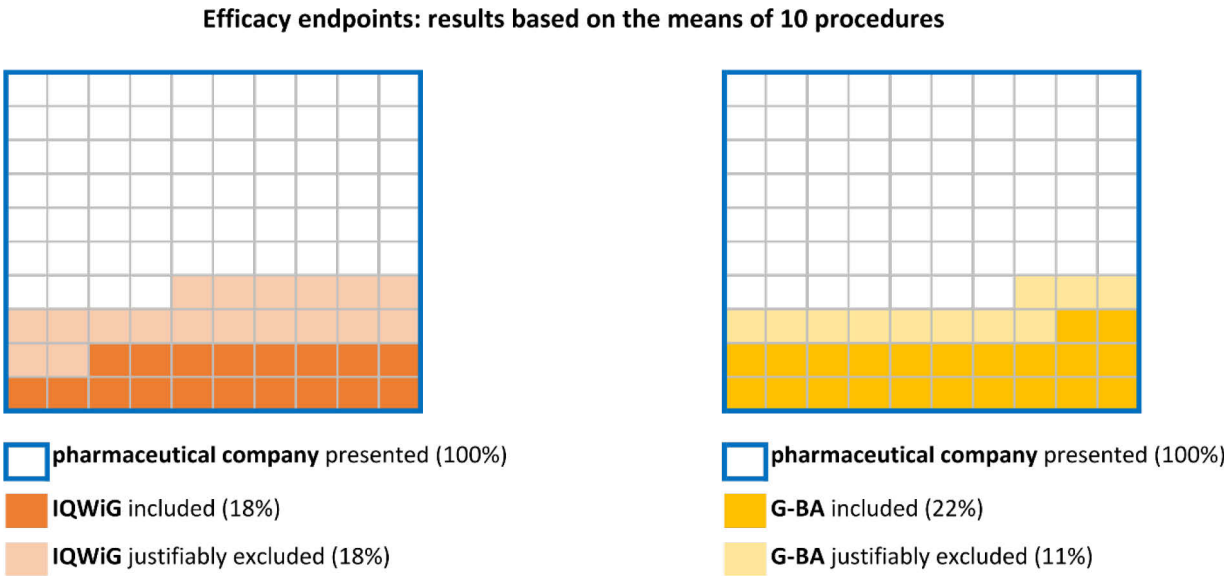

Figure 10: Proportion of efficacy endpoints (incl. sensitivity analyses) considered by IQWiG and G-BA

Note: The cited IQWiG and G-BA percentages are means of the relative proportions of the efficacy endpoints considered by the institutions.

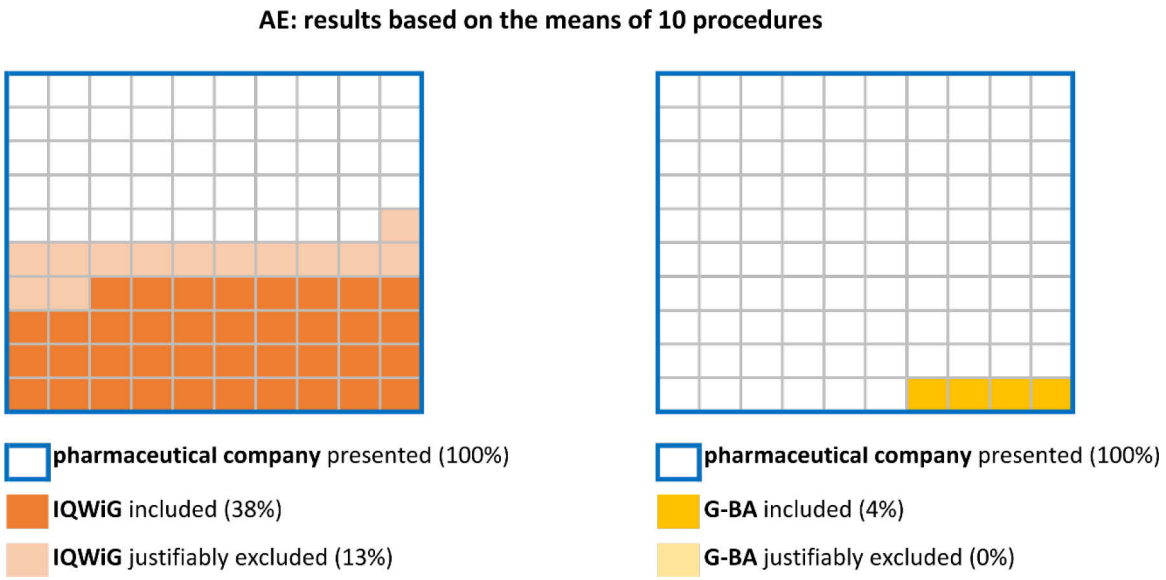

Figure 11: Proportion of AEs considered by IQWiG and G-BA

Note: The cited IQWiG and G-BA percentages are means of the relative proportions of the AEs considered by the institutions.

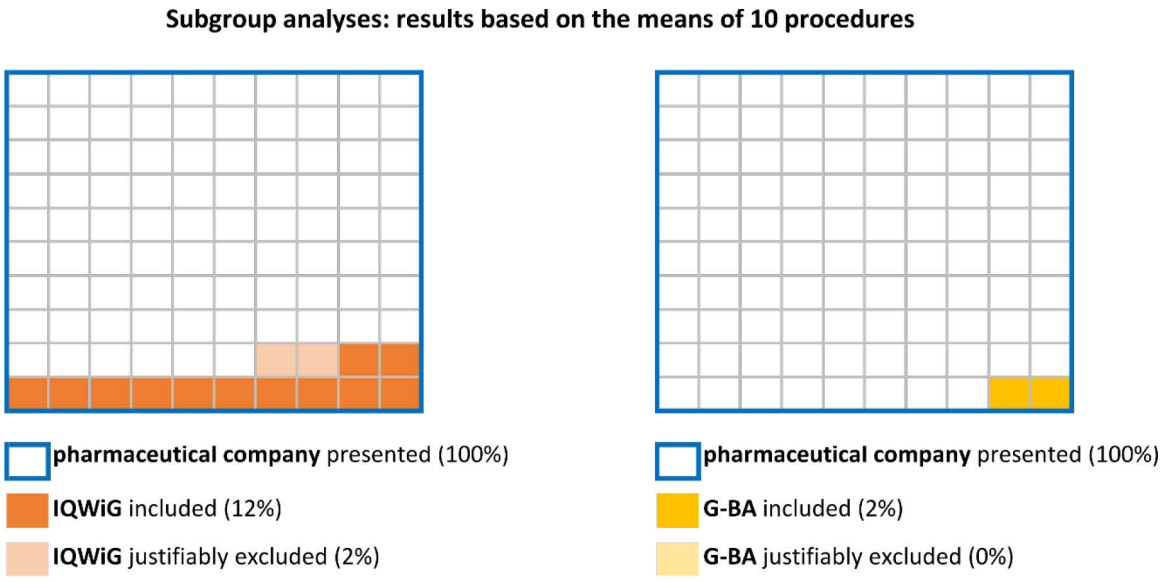

Figure 12: Proportion of subgroup analyses considered by IQWiG and G-BA

Note: The cited IQWiG and G-BA percentages are means of the relative proportions of the subgroup analyses considered by the institutions.

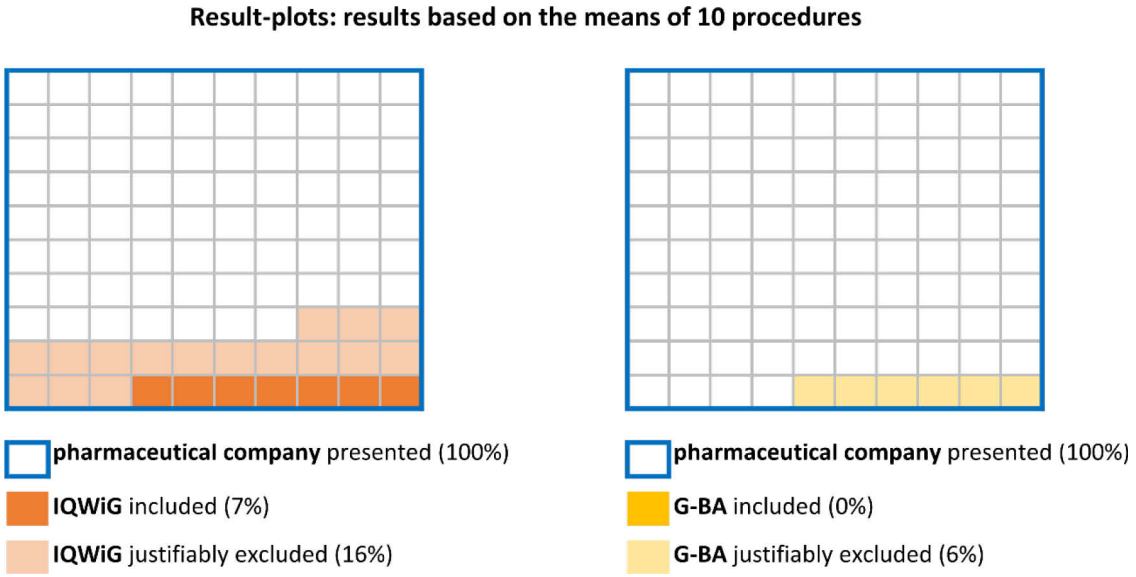

Figure 13: Proportion of result-plots considered by IQWiG and G-BA

Note: The cited IQWiG and G-BA percentages are means of the relative proportions of the result-plots considered by the institutions.

Tables

Table 3: Evaluations in the procedure Apalutamide (2020-04-01-D-538)

	Efficacy endpoints incl. sensitivity analyses	Adverse events	Subgroup analyses	Result-plots	Overall evaluations
Pharmaceutical company					
Evaluations presented	143	1,153	936	1,175	3,407
IQWiG					
Included evaluations	13 (9.1%)	269 (23.3%)	61 (6.5%)	18 (1.5%)	361 (10.6%)
Justifiably excluded evaluations	3 (2.1%)	0 (0.0%)	3 (0.3%)	16 (1.4%)	22 (0.6%)
G-BA					
Included evaluations	15 (10.5%)	11 (1.0%)	0 (0.0%)	1 (0.1%)	27 (0.8%)
Justifiably excluded evaluations	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
IQWiG and/or G-BA					
Included evaluations	15 (10.5%)	269 (23.3%)	61 (6.5%)	18 (1.5%)	363 (10.7%)
Justifiably excluded evaluations	3 (2.1%)	0 (0.0%)	3 (0.3%)	16 (1.4%)	22 (0.6%)

G-BA: Federal Joint Committee (Gemeinsamer Bundesauschuss); IQWiG: Institute for Quality and Efficiency in Health Care (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen)

Table 4: Evaluations in the procedure Brigatinib (2020-05-01-D-542)

	Efficacy endpoints incl. sensitivity analyses	Adverse events	Subgroup analyses	Result-plots	Overall evaluations
Pharmaceutical company					
Evaluations presented	40	155	632	210	1,037
IQWiG					
Included evaluations	15 (37.5%)	133 (85.8%)	171 (27.1%)	40 (19.0%)	359 (34.6%)
Justifiably excluded evaluations	1 (2.5%)	0 (0.0%)	3 (0.5%)	10 (4.8%)	14 (1.4%)
G-BA					
Included evaluations	17 (42.5%)	10 (6.5%)	81 (12.8%)	0 (0.0%)	108 (10.4%)
Justifiably excluded evaluations	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
IQWiG and/or G-BA					
Included evaluations	17 (42.5%)	133 (85.8%)	177 (28.0%)	40 (19.0%)	367 (35.4%)
Justifiably excluded evaluations	0 (0.0%)	0 (0.0%)	0 (0.0%)	10 (4.8%)	10 (1.0%)

G-BA: Federal Joint Committee (Gemeinsamer Bundesauschuss); IQWiG: Institute for Quality and Efficiency in Health Care (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen)

Table 5: Evaluations in the procedure Darolutamide (2020-05-01-D-543)

	Efficacy endpoints incl. sensitivity analyses	Adverse events	Subgroup analyses	Result-plots	Overall evaluations
Pharmaceutical company					
Evaluations presented	103	865	4,128	1,832	6,928
IQWiG					
Included evaluations	12 (11.7%)	165 (19.1%)	116 (2.8%)	9 (0.5%)	302 (4.4%)
Justifiably excluded evaluations	60 (58.3%)	506 (58.5%)	449 (10.9%)	1,421 (77.6%)	2,436 (35.2%)
G-BA					
Included evaluations	14 (13.6%)	6 (0.7%)	0 (0.0%)	0 (0.0%)	20 (0.3%)
Justifiably excluded evaluations	36 (35.0%)	0 (0.0%)	0 (0.0%)	75 (4.1%)	111 (1.6%)
IQWiG and/or G-BA					
Included evaluations	14 (13.6%)	165 (19.1%)	116 (2.8%)	9 (0.5%)	304 (4.4%)
Justifiably excluded evaluations	58 (56.3%)	506 (58.5%)	449 (10.9%)	1,421 (77.6%)	2,434 (35.1%)

G-BA: Federal Joint Committee (Gemeinsamer Bundesauschuss); IQWiG: Institute for Quality and Efficiency in Health Care (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen)

Table 6: Evaluations in the procedure Encorafenib (2020-07-01-D-551)

	Efficacy endpoints incl. sensitivity analyses	Adverse events	Subgroup analyses	Result-plots	Overall evaluations
Pharmaceutical company					
Evaluations presented	203	301	1,871	437	2,812
IQWiG					
Included evaluations	21 (10.3%)	173 (57.5%)	0 (0.0%)	6 (1.4%)	200 (7.1%)
Justifiably excluded evaluations	65 (32.0%)	0 (0.0%)	0 (0.0%)	90 (20.6%)	155 (5.5%)
G-BA					
Included evaluations	22 (10.8%)	6 (2.0%)	0 (0.0%)	0 (0.0%)	28 (1.0%)
Justifiably excluded evaluations	65 (32.0%)	0 (0.0%)	0 (0.0%)	90 (20.6%)	155 (5.5%)
IQWiG and/or G-BA					
Included evaluations	22 (10.8%)	173 (57.5%)	0 (0.0%)	6 (1.4%)	201 (7.1%)
Justifiably excluded evaluations	65 (32.0%)	0 (0.0%)	0 (0.0%)	90 (20.6%)	155 (5.5%)

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Table 7: Evaluations in the procedure Enzalutamide (2020-05-15-D-541)

	Efficacy endpoints incl. sensitivity analyses	Adverse events	Subgroup analyses	Result-plots	Overall evaluations
Pharmaceutical company					
Evaluations presented	6	405	735	110	1,256
IQWiG					
Included evaluations	1 (16.7%)	249 (61.5%)	191 (26.0%)	9 (8.2%)	450 (35.8%)
Justifiably excluded evaluations	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
G-BA					
Included evaluations	2 (33.3%)	9 (2.2%)	0 (0.0%)	0 (0.0%)	11 (0.9%)
Justifiably excluded evaluations	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
IQWiG and/or G-BA					
Included evaluations	2 (33.3%)	249 (61.5%)	191 (26.0%)	9 (8.2%)	451 (35.9%)
Justifiably excluded evaluations	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

G-BA: Federal Joint Committee (Gemeinsamer Bundesauschuss); IQWiG: Institute for Quality and Efficiency in Health Care (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen)

Table 8: Evaluations in the procedure Fidaxomicin (2020-03-15-D-519)

	Efficacy endpoints incl. sensitivity analyses	Adverse events	Subgroup analyses	Result-plots	Overall evaluations
Pharmaceutical company					
Evaluations presented	32	111	412	16	571
IQWiG					
Included evaluations	6 (18.8%)	48 (43.2%)	100 (24.3%)	2 (12.5%)	156 (27.3%)
Justifiably excluded evaluations	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
G-BA					
Included evaluations	6 (18.8%)	7 (6.3%)	13 (3.2%)	0 (0.0%)	26 (4.6%)
Justifiably excluded evaluations	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
IQWiG and/or G-BA					
Included evaluations	6 (18.8%)	48 (43.2%)	100 (24.3%)	2 (12.5%)	156 (27.3%)
Justifiably excluded evaluations	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

G-BA: Federal Joint Committee (Gemeinsamer Bundesauschuss); IQWiG: Institute for Quality and Efficiency in Health Care (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen)

Table 9: Evaluations in the procedure Ozanimod (2020-07-15-D-567)

	Efficacy endpoints incl. sensitivity analyses	Adverse events	Subgroup analyses	Result-plots	Overall evaluations
Pharmaceutical company					
Evaluations presented	123	131	675	360	1,289
IQWiG					
Included evaluations	52 (42.3%)	8 (6.1%)	90 (13.3%)	2 (0.6%)	152 (11.8%)
Justifiably excluded evaluations	8 (6.5%)	97 (74.0%)	48 (7.1%)	108 (30.0%)	261 (20.2%)
G-BA					
Included evaluations	52 (42.3%)	20 (15.3%)	0 (0.0%)	0 (0.0%)	72 (5.6%)
Justifiably excluded evaluations	8 (6.5%)	0 (0.0%)	0 (0.0%)	43 (11.9%)	51 (4.0%)
IQWiG and/or G-BA					
Included evaluations	52 (42.3%)	20 (15.3%)	90 (13.3%)	2 (0.6%)	164 (12.7%)
Justifiably excluded evaluations	8 (6.5%)	85 (64.9%)	48 (7.1%)	108 (30.0%)	249 (19.3%)

G-BA: Federal Joint Committee (Gemeinsamer Bundesauschuss); IQWiG: Institute for Quality and Efficiency in Health Care (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen)

Table 10: Evaluations in the procedure Romosozumab (2020-03-15-D-516)

	Efficacy endpoints incl. sensitivity analyses	Adverse events	Subgroup analyses	Result-plots	Overall evaluations
Pharmaceutical company					
Evaluations presented	146	1,528	1,012	50	2,736
IQWiG					
Included evaluations	10 (6.8%)	278 (18.2%)	22 (2.2%)	10 (20.0%)	320 (11.7%)
Justifiably excluded evaluations	63 (43.2%)	0 (0.0%)	17 (1.7%)	8 (16.0%)	88 (3.2%)
G-BA					
Included evaluations	25 (17.1%)	42 (2.7%)	0 (0.0%)	0 (0.0%)	67 (2.4%)
Justifiably excluded evaluations	5 (3.4%)	0 (0.0%)	0 (0.0%)	8 (16.0%)	13 (0.5%)
IQWiG and/or G-BA					
Included evaluations	25 (17.1%)	313 (20.5%)	22 (2.2%)	10 (20.0%)	370 (13.5%)
Justifiably excluded evaluations	57 (39.0%)	0 (0.0%)	17 (1.7%)	8 (16.0%)	82 (3.0%)

G-BA: Federal Joint Committee (Gemeinsamer Bundesauschuss); IQWiG: Institute for Quality and Efficiency in Health Care (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen)

Table 11: Evaluations in the procedure Talazoparib (2020-06-01-D-545)

	Efficacy endpoints incl. sensitivity analyses	Adverse events	Subgroup analyses	Result-plots	Overall evaluations
Pharmaceutical company					
Evaluations presented	143	361	2,090	552	3,146
IQWiG					
Included evaluations	21 (14.7%)	153 (42.4%)	102 (4.9%)	32 (5.8%)	308 (9.8%)
Justifiably excluded evaluations	48 (33.6%)	0 (0.0%)	50 (2.4%)	48 (8.7%)	146 (4.6%)
G-BA					
Included evaluations	22 (15.4%)	17 (4.7%)	0 (0.0%)	0 (0.0%)	39 (1.2%)
Justifiably excluded evaluations	48 (33.6%)	0 (0.0%)	0 (0.0%)	48 (8.7%)	96 (3.1%)
IQWiG and/or G-BA					
Included evaluations	22 (15.4%)	153 (42.4%)	102 (4.9%)	32 (5.8%)	309 (9.8%)
Justifiably excluded evaluations	48 (33.6%)	0 (0.0%)	50 (2.4%)	48 (8.7%)	146 (4.6%)

G-BA: Federal Joint Committee (Gemeinsamer Bundesauschuss); IQWiG: Institute for Quality and Efficiency in Health Care (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen)

Table 12: Evaluations in the procedure Trifluridine/Tipiracil (2020-04-01-D-535)

	Efficacy endpoints incl. sensitivity analyses	Adverse events	Subgroup analyses	Result-plots	Overall evaluations
Pharmaceutical company					
Evaluations presented	38	923	4,687	10,521	16,169
IQWiG					
Included evaluations	3 (7.9%)	253 (27.4%)	512 (10.9%)	44 (0.4%)	812 (5.0%)
Justifiably excluded evaluations	0 (0.0%)	6 (0.7%)	12 (0.3%)	60 (0.6%)	78 (0.5%)
G-BA					
Included evaluations	6 (15.8%)	22 (2.4%)	0 (0.0%)	0 (0.0%)	28 (0.2%)
Justifiably excluded evaluations	0 (0.0%)	6 (0.7%)	0 (0.0%)	60 (0.6%)	66 (0.4%)
IQWiG and/or G-BA					
Included evaluations	6 (15.8%)	253 (27.4%)	512 (10.9%)	44 (0.4%)	815 (5.0%)
Justifiably excluded evaluations	0 (0.0%)	6 (0.7%)	12 (0.3%)	60 (0.6%)	78 (0.5%)

G-BA: Federal Joint Committee (Gemeinsamer Bundesauschuss); IQWiG: Institute for Quality and Efficiency in Health Care (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen)