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German AMNOG Benefit Assessment in the Field of Oncology: Factors Influencing the Benefit Rating in Addition to the Appropriate Comparator

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Background

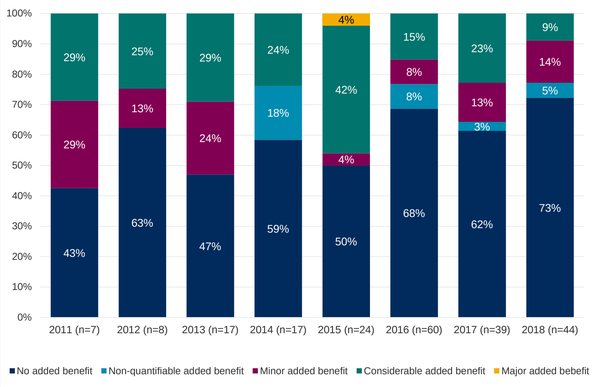
- For benefit assessment of new pharmaceuticals in Germany, the Federal Joint Committee (FJC) defines appropriate comparators of 4 categories: (1) one specific drug, (2) a list of drugs, (3) patient individual therapy, and (4) best supportive care.
- To have an added benefit granted by the FJC, it is essential for pharmaceutical companies to provide comparative evidence against the assigned appropriate comparator.
- According to the FJC's rules of procedure, 6 categories for an added benefit can be assigned: major, considerable, minor, no, less, and non-quantifiable. A non-quantifiable added benefit can be used if the underlying evidence is highly biased and/or decision uncertainty is high.
- The assigned category of added benefit is a decisive factor that influences the outcome of the price negotiation for new pharmaceuticals with the National Association of Statutory Health Insurance Funds (GKV-Spitzenverband).
- The FJC can commission the Institute for Quality and Efficiency in Health Care (IQWiG) as an independent specialist scientific institution to carry out the early benefit evaluation. For assessment of the cost-benefit relation of new pharmaceuticals the IQWiG provides General Methods summarizing the applied scientific standards.
- If no added benefit is identified by the FJC, the new pharmaceutical is allocated to a reference price group comprising comparable active ingredients.

Objectives and Methods

- The aim of the study was to evaluate factors that lead to a negative benefit rating in oncological Pharmaceuticals Market Reorganization Act (AMNOG) assessments.
- Information was retrieved from all non-orphan AMNOG dossiers in the field of oncology published on the FJC website (https://www.g-ba.de) until the end of 2018.
- Information regarding indication, appropriate comparator, and outcomes was obtained. In addition, it was determined if the comparator used in the relevant clinical trials was accepted as appropriate by the FJC.
- Furthermore, dossiers that complied with the assigned appropriate comparator by the FJC and were rated with "no added benefit" were further analyzed for the reasons leading to the negative outcome of the benefit assessment.

Results

Figure 1. The Likelihood of Gaining an Added Benefit Decreased Over the Years



- 110 AMNOG dossiers in the field of oncology were published between 2011 and 2018 that were conclusively assessed by the FJC. These dossiers included 216 separately evaluated labels and sub labels.
- The chance to gain an added benefit was highest in the first year of AMNOG (~58%) and fluctuated around ~45% between 2012 and 2015 (**Figure 1**).
- From 2016 onward, the proportion of assessments resulting in no added benefit clearly increased, with a maximum of 73% in 2018, pointing toward a reduced likelihood for a positive benefit rating in comparison to previous years (**Figure 1**).
- Strikingly, the assignment of a non-quantifiable added benefit became more frequent in recent years, from 2016 to 2018 (with exception of 2014) (**Figure 1**).
- When considering all AMNOG dossiers in the field of oncology, the assignment of appropriate comparators by the FJC was distributed as follows:
  - The most commonly assigned appropriate comparator was a list of drugs (40%) (**Figure 2**).
  - The categories specific drug (24%), patient individual therapy (16%), and best supportive care (20%) were almost evenly distributed (**Figure 2**).

Figure 2. A List of Drugs Is the Most Commonly Assigned Category of Appropriate Comparator

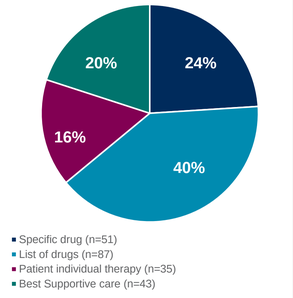
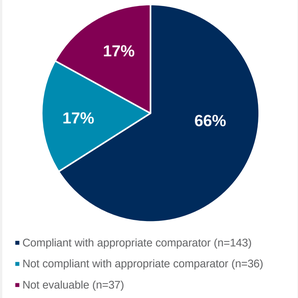
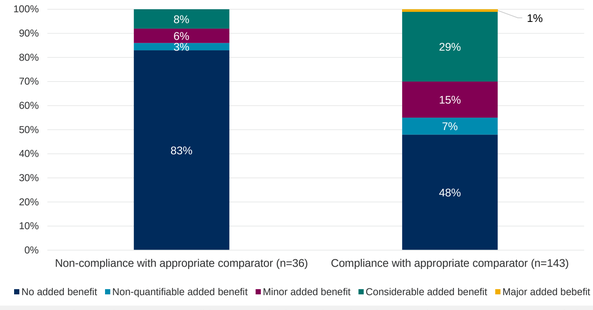


Figure 3. In the Majority of Cases, the Study Comparator Complied With FJC's Requirements



- In 143 (66%) of 216 assessments of labels and sub labels, the study comparator did comply with the assigned appropriate comparator by the FJC. (**Figure 3**).
- 36 (17%) of the 216 cases did not comply with the FJC's assignment of appropriate comparator (**Figure 3**).
- 37 (17%) of the 216 assessments could not be allocated to one category because the dossiers presented single-arm studies or did not contain any data for the FJC's defined target population . (**Figure 3**).

Figure 4. Compliance With the Appropriate Comparator Is Crucial for a Positive Benefit Rating

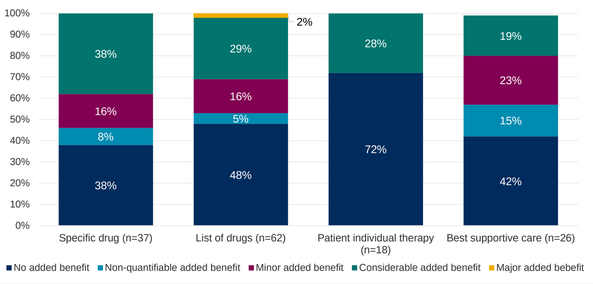


- In case the study comparator did not match the FJC-assigned appropriate comparator, most of the assessments resulted in no added benefit (83%) (**Figure 4**). Nevertheless, it does not generally preclude an added benefit to be granted.
- So far, not a single assessment in the setting of non-compliance with the assigned appropriate comparator gained a major added benefit (**Figure 4**).

Results (cont.)

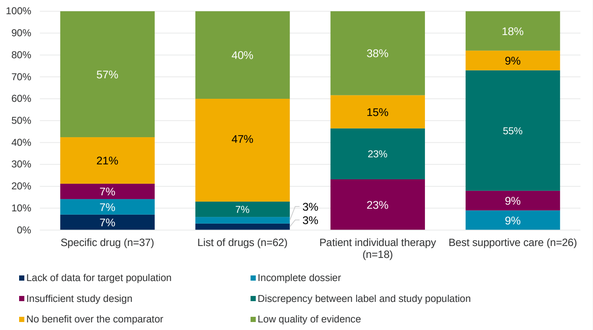
- In 143 assessments, the study comparator was accepted by the FJC as appropriate comparator. However, only 52% of the cases gained an added benefit, distributed as follows: non-quantifiable (7%), minor (15%), considerable (29%), and major (1%) (**Figure 4**).
- Remarkably, 68 assessments (48%) that did comply with the assigned appropriate comparator resulted in no added benefit (**Figure 4**).

Figure 5. The Outcome of the Benefit Assessment Differs Between the Categories of Appropriate Comparators



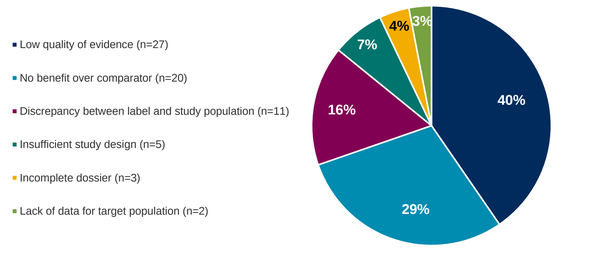
- All 143 assessments that did comply with the FJC-assigned appropriate comparator were analyzed for the correlation of the category of appropriate comparator and the outcome of the benefit assessment (**Figure 5**).
- If data against the assigned appropriate comparator were presented, the chance to gain an added benefit was similarly distributed between the categories "specific drug" (62%), "list of drugs" (50%), and "best supportive care" (57%) (**Figure 5**).
- A major added benefit was only achieved in the category "list of drugs" (**Figure 5**).
- Compliance with the appropriate comparator category "patient individual therapy" only resulted in 28% of cases in a positive outcome, with a considerable added benefit in all cases (**Figure 5**).

Figure 6. The Reasons for the Negative Benefit Rating Can Be Linked With the Specific Challenges of Each Appropriate Comparator Category



- To identify further factors influencing the benefit rating, the 68 assessments that complied with the assigned appropriate comparator by the FJC but still did not gain an added benefit were analyzed (**Figure 6**).
- The distribution of reasons for a negative benefit rating by the FJC differs between the categories of assigned appropriate comparators and can be explained by specific challenges of each category:
  - The most prominent reason for a negative benefit rating in the comparator category "specific drug" is a low quality of evidence (**Figure 6**). This mainly results from the attempts to show indirect evidence against the appropriate comparator. The resulting indirect treatment comparison was often not sufficient with respect to the strict IQWiG requirements to gain an added benefit.
  - In the category "list of drugs," the chance to comply with the appropriate comparator is comparatively high. The main reasons for negative outcomes of benefit assessments were the lack of any advantage of the new pharmaceutical over the comparator in patient-relevant endpoints or a negative harm-benefit ratio (**Figure 6**).
  - The comparator "patient individual therapy" in clinical studies often does not fulfill IQWiG requirements regarding choice of drugs according to German guidelines or allocation of patients (**Figure 6**).
  - The discrepancy between label and study population plays a major role in the negative benefit rating within the categories "patient individual therapy" (23%) and "best supportive care" (55%) (**Figure 6**). The FJC often defines the types of appropriate comparators for certain subpopulations (eg, high-risk patients, patients in palliative setting). In these indications, the study population does not necessarily reflect the label population.

Figure 7. Low Quality of Evidence Is the Major Reason for No Added Benefit Despite Compliance With the Appropriate Comparator



- Overall, the major reason for the negative benefit outcome was low quality of evidence (40%). This was mostly due to the attempt to meet the appropriate comparator using indirect comparisons, which were often considered inadequate by IQWiG and FJC (**Figure 7**).
- In 29% of cases, no advantage of the new pharmaceutical over the comparator in patient-relevant endpoints or a negative harm-to-benefit ratio in relation to the appropriate comparator was shown (**Figure 7**).
- Furthermore, the discrepancy between label and study population and an insufficient study design were the reason for no added benefit by the FJC in 16% and 7% of the assessments, respectively (**Figure 7**).
- Only in 3 of 68 cases (4%), no added benefit was assigned due to the submission of an incomplete dossier (**Figure 7**). The reasons for incompleteness comprised missing subgroup analysis and the lack of research for relevant studies in clinical trial registries. In one assessment, the target population was a subgroup of the study population and a tailored analysis was not presented.
- The lack of data for the target population was the determining factor for no added benefit in 2 of 68 cases (3%) (**Figure 7**). In both cases, the FJC further subdivided the target population for the derivation of the added benefit, and the resulting subpopulation was not covered by the respective clinical trials.

Conclusions

- The appropriate comparator assigned by FJC significantly influences the outcome of the AMNOG benefit assessment - which further affects the following price negotiation of new pharmaceuticals.
- Non-compliance with the assigned appropriate comparator by the FJC almost always resulted in no added benefit. Nevertheless, compliance is no guarantee for an added benefit, since almost half of the assessments also ended up with no added benefit over the comparator.
- Further factors were identified that play a decisive role in the outcome of the benefit rating: low quality of evidence, no benefit over the comparator, discrepancy between study and label population, insufficient study design, incomplete dossier, and lack of data for target population.
- The distribution of factors leading to a negative benefit outcome reflects the specific challenges in each category of appropriate comparators to gain an added benefit.
- Overall, the major reasons for a negative benefit rating despite complying with the appropriate comparator were low quality of evidence (40%) and no benefit over the comparator (29%).

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