Oncological combination therapies in the context of the early benefit assessment according to AMNOG – status quo and quo vadis

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Objectives

In recent years, there has been a noticeable proliferation of combinatorial therapeutic approaches within the field of oncology. These approaches encompass a wide array of drug combinations meticulously designed to optimize their therapeutic effectiveness. [1] Nevertheless, this development has ignited a contentious debate, particularly concerning the associated financial outlays. [2, 3] Following the implementation of the German Medicines Reorganization Act (AMNOG) in 2011, the pricing of pharmaceutical products is no longer determined directly by manufacturers; instead, it is subjected to rigorous regulatory oversight. [4] One year after a new drug receives market approval in Germany, its pricing is established through negotiations between the pharmaceutical company and the National Association of Statutory Health Insurance Funds. This pricing process is rooted in the AMNOG framework and is closely tied to the early benefit assessment (EBA), which evaluates the drug's effectiveness and advantages. The resulting reimbursement price serves as the foundation for payments made by statutory health insurance funds. [5] The primary objective of our research was to undertake a methodological analysis of the combination therapies employed in the field of oncology, as assessed thus far within the framework of the EBA.

Methods

In this study, we conducted a systematic extraction of the temporal progression and additional benefits attributed by pharmaceutical companies (pC), the Institute for Quality and Efficiency in Health Care (IQWiG), and the Federal Joint Committee (G-BA). A central aspect of our investigation was the systematic identification of the rationales behind claims of added or no added benefit, while carefully considering methodological challenges. Furthermore, we sought to identify key factors contributing to success and anticipated future trends in this domain.
While assessing these factors to ensure reproducibility, a structured methodology was employed. Data inclusion was contingent upon alignment with the predefined inclusion criteria as delineated in Table 1. Subsequently, a raw data table was constructed, facilitating the extraction of fundamental information from the evaluated assessments. To establish a comprehensive meta data table, a combination of evaluation tools was applied, as per the guidelines stipulated in the German Drug Benefit Regulation (AM-NutzenV) for the evaluation of the extent, with additional probability assessment tools provided by the G-BA. In addition to these tools, a set of evaluation metrics aimed at identifying methodological challenges was devised, drawing upon shared characteristics and the potential for aggregating research data, all of which are outlined in Table 2. Concurrently, a comprehensive analysis was conducted to ascertain both the methodological challenges and success factors pertinent to specific endpoints, namely, overall survival (OS), progression-free survival (PFS), health status, symptoms, health-related quality of life (HRQoL), and the occurrence of side effects.

Inclusion criteria	
I1	All data are taken from the G-BA homepage
I2	Only completed procedures are included
I3	Data cut.off: 28th of Feburary 2023
I4	Modul 4 of manufactures dossier must be available
I5	IQWiG's benefit assessment (if applicable additionally the addendums) must be available
I6	G-BA main reason for the decisions must be available

Table 1: Inclusion Criteria set

Evaluation wording	Description
	General
no/not enough data	Due to a lack of data, the assessment of an additional benefit is not possible, which has an impact on the overall benefit
no adequate implementation of the assessment	No adequate implementation of the evaluation (pC did not use the appropriate comparator therapy defined by the G-BA)
	Evaluation not possible for study comparison, as measurement instruments/study design etc. are different among comparing studies
Unratable	Due to the lack of scientific data, it is not possible to evaluate the additional benefits. This has a direct impact on the overall added value
high distortion bias	There is a high potential for bias, which affects the probability of evidence and has a direct negative impact on the assessment of the overall added benefit
a previously unattained large improvement in therapy-relevant benefits	A previously unachieved significant improvement in therapy-relevant benefit
None	Combination therapy is the first in the indication area
	No problems present
	Positive
meaningful advantages	Advantages outweigh disadvantages due to statistically significant and/or meaningful advantages
beneficial effects	Positive effects are present, but they do not outweigh the disadvantages
	Negative
meaningful disadvantages	Disadvantages outweigh advantages due to statistically significant and/or meaningful disadvantages
harmful effects	In terms of AE & SAEs: are nevertheless still well treatable and known significant greater harm
low negative effects	Negative effects are present, but they do not outweigh the advantages
	In terms of AE & SAEs: The assessment does not downgrade the overall assessment

Table 2: Aggregated wording for the identification of the methodological challenges (IQWiG, and G-BA)

Conclusions

Oncological combination therapies are on the rise. However, added benefit decreases over time and suggests that submitted data decreases in quality and validity. In order to counteract this development, valid data, especially on HRQoL and AEs is needed. These endpoint categories may be success factors for the future. It is anticipated that costs of oncological combination therapies will continue to rise significantly, a trend that should go with convincing data.

Results

Basic data

In the context of early benefit assessments (EBA), a total of 74 evaluations were conducted within the realm of oncological combination therapies. However, only 73 benefit assessments were taken into consideration for the final evaluation due to an exclusion of a faulty file. A disparity emerged as a result of the compelling necessity to delineate patient cohorts with precision, consequently resulting in a notably elevated aggregate of individual benefit assessments. [6] Consequently, this culminated in a cumulative total of 103 individual benefit assessments originating from pCs, 130 assessments from the IQWiG and 135 assessments conducted by the G-BA.

Therapeutic areas

As part of our investigation into the frequency of therapy options in various therapeutic areas, we found that a total of 37 benefit assessments were performed in the area of breast cancer, corresponding to a proportion of 50 percent. This result can be primarily attributed to the high prevalence of breast cancer. In 2018, approximately 600,000 women in Germany were either diagnosed with breast cancer or had a history of the disease. [7, 8]
This also applies to the field of melanoma and renal cell carcinoma which were conducted ten and eight times in terms of benefit assessments. Both therapeutic areas have a comparatively high prevalence and death rate as well. The remaining 19 benefit assessments (25.6 percent) were in various other therapeutic areas.

Active substances

When evaluating the frequency of the active substances evaluated, it should be noted that these results are consistent with the results of the therapeutic areas. Nivolumab and Pembrolizumab each underwent extensive evaluation in a total of 11 times, making them the most frequently analyzed agents in the content of EBA. Both substances find application in the therapy of melanoma. [9]

Extent of additional benefit

With regard to Figure 1, when comparing the awards of the benefit assessments by pCs, IQWiG, and G-BA, it's clear that pCs assessed most potential benefits, while IQWiG and G-BA had more evaluations with no demonstrated additional benefits. Focusing on G-BA decisions, in total 135 subpopulations showed predominantly no added benefit (41%). Differences in assessment methods, criteria, data sources, and treatment types contributed to these variations. Evaluating treatment efficacy is complex and varies between assessment authorities due to numerous factors.

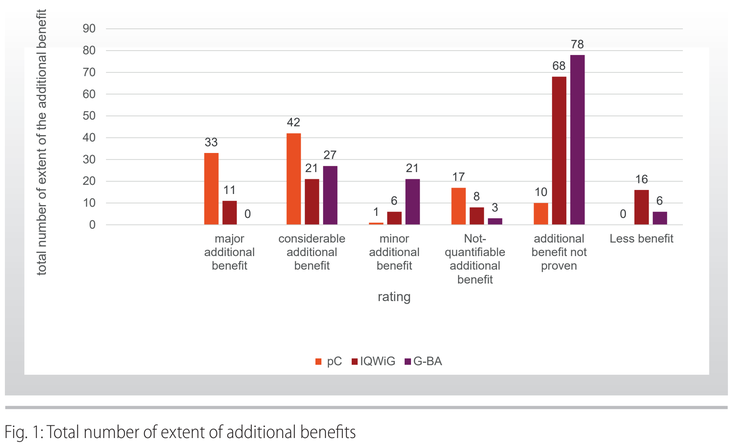

Fig. 1: Total number of extent of additional benefits

Probability of additional benefit

Generally, as seen in Figure 2, pCs tend to have more optimistic probability estimations compared to those of IQWiG and the G-BA.

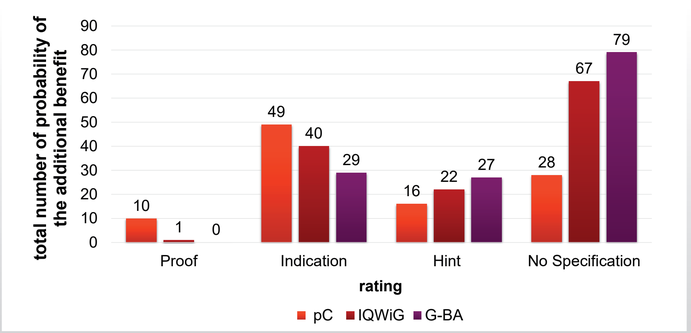

Fig. 2: Total number of probability of additional benefits

Methodological challenges

In the assessment of oncological combination therapies by the G-BA and the IQWiG several methodological challenges have emerged (see Table 3). One significant issue is the difficulty in clearly identifying discriminating features, especially in the context of relevant endpoints. The validity of PFS as a key endpoint has come into question, as it may not always reflect meaningful clinical benefits. Moreover, data on HRQoL and AEs have presented major hurdles. In many cases, HRQoL data are either missing or challenging to interpret, making it difficult to assess the impact of therapies on patients' well-being. Similarly, non-interpretable data on AEs has complicated the evaluation of therapy safety and tolerability. These challenges have had a substantial impact on decision-making. In some instances, the data on HRQoL have outweighed perceived additional benefits, leading to the withholding of additional benefits in 11 cases. Additionally, non-interpretable data on AEs has influenced decisions in four cases, potentially affecting the overall benefit assessment.
Addressing these methodological challenges is crucial to ensure a comprehensive and transparent evaluation of oncological combination therapies, ultimately determining their potential benefits to patients.

General	- G-BA and IQWiG adress the issues which led to granting or non-granting of additional benefit but - Clear determination of discriminating features in context of endpoints not possible
Major decision-making challenges due to	- The validity of progression-free survival, missing or non-interpretable data on Health-Related Quality of Life (HRQoL) and non-interpretable data on adverse events (AEs) - When data on HRQoL and AEs were assessed, they outweighed added benefit in four, respectively eleven cases

Table 3: Methodological challenges

Success factors

The assignment of an added benefit for oncological combination therapies is a complex process that is influenced by various factors. In this context, several key aspects have to be considered, which are decisive in determining whether such a therapy is considered superior to conventional treatments. The availability of data on OS, study type (randomized vs. non-randomized), and endpoints like PFS and HRQoL are key factors in assessing the level of additional benefit. The severity of the disease and the availability of alternative treatments also influence the assessment. Adverse effects/events (AE) can reduce the perceived benefit, and a thorough analysis of clinical trial data is essential for accurate conclusions.

Timeline of additional benefit and future trends

In recent years, there has been a noticeable change in how additional benefits are granted. Since 2016, the number of individual benefit assessments that have been denied additional benefits has significantly increased, surpassing the number of assessments where additional benefits were granted. This trend can be observed in Figure 3. It's unclear why this increase in benefit denials and contributions occurred, as there were no new benefits introduced during this time. One possibility is that changes in the legal climate or assessment criteria may be a factor. The G-BA frequently adjusts its procedural rules to align with current research and legal circumstances. [10]

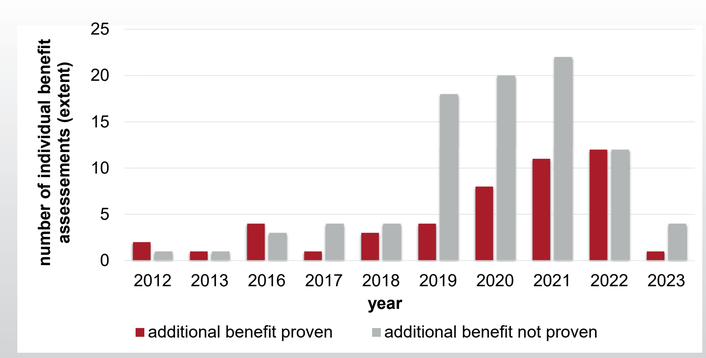

Fig. 3: Total number of individual benefit assessments which either had an additional benefit or not over the years since 2011

Future trends considering price development

The 2021 study by Gothe et al. shows that the total cost of cancer therapies has increased in recent years due to the demand for more expensive and effective therapies. In particular, the cost of combination therapy with Pembrolizumab and chemotherapy for advanced non-small cell lung cancer increased by 100 percent between 2016 and 2019, from about 10,000 euros to almost 20,000 euros. The study analyzes the average cost per patient treated for combination therapies from 2012 to 2018 and shows that costs have increased continuously. In 2012, the median cost per patient was about €8,000, while in 2018 it increased to about €11,800, a 47.5 percent increase. Particularly sharp cost increases occurred in 2016 and 2017, when costs were about 10,900 euros and 11,300 euros, respectively. The authors concluded that the cost of cancer treatments, particularly brand-new and cutting-edge treatments, will continue to increase into the foreseeable future. However, they also emphasize that it is important to consider costs in the con-text of the clinical benefit of therapy to guarantee that patients will receive the appropriate treatment. [11]

One possible solution? SHI financial stabilization act Response of German Government

On October 28, 2022, the German Federal Council approved the concept of the combination discount, which was created in response to the rising costs of combination therapies. Under Section 130e of the Fifth Book of the German Social Code (SGB V), health insurers will receive a discount from pCs if they supply new drug combinations after May 2, 2023. The discount amounts to 20 percent of the pC's sales price excluding VAT. This discount does not apply if the G-BA determines an additional benefit for the combination of drugs. [12]

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