An analysis of case studies

# Unproven added benefit due to late changes to the appropriate comparator therapy

As part of the early benefit assessment, the added benefit of new medicinal products protected by documentation is assessed in comparison to the appropriate comparator therapy (ACT). At the request of the pharmaceutical company (MAH), the Federal Joint Committee (G-BA) discusses the documents to be submitted and the ACT. The G-BA can adjust the zVT determined in the course of a consultation over time. This can also be done after the start of a benefit assessment. In this paper, examples are presented that show how the change of the zVT in the ongoing benefit assessment procedure can lead to a usable randomised controlled trial (RCT) not being considered by the G-BA, which in turn leads to an unproven added benefit. Results: In this analysis, four practical cases were presented in which the manufacturer was confronted with the situation of an unsuitable study comparator due to a zVT amendment in the ongoing benefit assessment procedure. For example, drugs for the treatment of head and neck tumours, multiple sclerosis or chronic rhinosinusitis were denied the additional benefit initially determined by the Institute for Efficiency and Quality in Health Care (IQWiG) in the procedure in the final G-BA decision due to short-term changes to the zVT.

>> The benefit assessment, introduced in 2011 by the Act on the Reform of the Market for Medicinal Products (AMNOG), has led to a structured assessment of new medicinal products as part of the price regulation procedure (1).

As part of the benefit assessment, every new medicinal product that has been tested and authorised for quality, efficacy and safety in the approval procedure is assessed for its additional benefit in comparison to already established treatment options (1). The appropriate comparator therapy (ACT) plays a central role in the benefit assessment and serves as the basis for the assessment of the added benefit of new drugs.

The results of the benefit assessment are assigned to six categories: substantial, considerable, minor, non-quantifiable additional benefit, additional benefit not proven, minor benefit (2). The benefit assessment of a medicinal product is decisive for the downstream price negotiation between the pharmaceutical company (MAH) and the National Association of Statutory Health Insurance Funds (GKV-SV). Medicinal products with unproven additional benefits are either assigned to a reference price group or a reimbursement amount is agreed that should not exceed the annual therapy costs of the most economical zVT (3, 4). The SHI Financial Stabilisation Act (GKV-FinStG) of November 2022 stipulates (despite exceptions under the Medical Research Act) that medicinal products with unproven additional benefits that have been assessed exclusively against a patent- or document-protected cVT must agree a reimbursement amount that is at least 10 percent below the most cost-effective cVT (5).

## G-BA consultation

At the request of the company, the G-BA advises on specific content for the dossier for the benefit assessment, on clinical trials and on the CVT. Since the Act for More Safety in the Supply of Medicinal Products (GSAV) came into force in 2019, the scope of the G-BA consultation has been expanded. The scientific and medical societies and the Drug Commission of the German Medical Association (AkdÄ) are to be involved in writing on questions relating to cVT (6).

## Selection of the appropriate comparator therapy

The regular determination of the zVT is based, among other things, on criteria derived from the international standards of evidence-based medicine. The preferred therapy should correspond to currently recognised medical knowledge and preferably be based on endpoint studies and proven practical application (2).

A CVT advised by the G-BA can be adapted over time by the G-BA (7). A change to the CVT can be made at any time, for example a few months after a consultation by the G-BA, during an ongoing clinical trial with the advised comparator therapy (as comparator) or during an ongoing benefit assessment procedure (7).

## Criteria for the identification of case studies

Three criteria were defined for the exemplary identification of relevant examples. The first criterion is the time of the switch of the zVT. For this purpose, only those benefit assessments were considered for the present analysis in which a change of CVT occurred during the assessment process between day 1 of the benefit assessment and the day of the final decision on the benefit assessment by the G-BA. Changes of zVT occurring at any other time (e.g. the frequent case between early consultation and start of benefit assessment) were excluded.

The second criterion concerns deviations between the additional benefit recommendation of the Institute for Quality and Efficiency in Health Care (IQWiG) and the final decision of the G-BA. For the present analysis, only benefit assessment procedures were considered in which IQWiG had attested an added benefit, but the G-BA decided on a non-proven added benefit due to the zVT

| Übersicht der Nutzenbewertungsverfahren mit einem zVT-Wechsel | | | |
|---|---|---|---|
| **Wirkstoff** | **Handelsname** | **Beschlussfassung (Jahr)** | **Indikation** |
| Pembrolizumab | Keytruda | 2019 | Plattenepithelkarzinom (Kopf-Hals-Bereich, HNSCC)[8] |
| Ozanimod | Zeposia | 2021 | Multiple Sklerose[9] |
| Mepolizumab | Nucala | 2022 | Chronische Rhinosinusitis mit Nasenpolypen[10] |
| Dimethylfumarat | Tecfidera | 2024 | Multiple Sklerose[11] |

***Table 1:*** *Overview of the benefit assessment procedures with a change of zVT in the ongoing procedure that led to the result 'unproven added benefit'.*

amendment.

The third criterion refers to the studies presented by the company. Only cases with directly comparative, randomised controlled trials (RCTs) were included. In addition, the benefit assessment procedures had to have been completed between 2011 and 2024.

## Results

On the basis of the inclusion criteria described, 4 real-life cases were identified and analysed in detail (Table 1).

**Case: Pembrolizumab (trade name: Keytruda) in squamous cell carcinoma (head and neck, HNSCC)**

In the present case of pembrolizumab in the indication HNSCC, the zVT 'patient-specific therapy of the physician's choice' was determined on the basis of a consultation meeting held with the G-BA in September 2014 (12).

In IQWiG's benefit assessment of pembrolizumab in 2019, 'patient-individualised therapy of the doctor's choice' continued to be used as the zVT. However, the G-BA changed this to nivolumab after the oral hearing. This change was justified by the opinions of the specialist societies represented. According to these, nivolumab was available as a treatment option at the time and was preferable to other treatment options. The G-BA therefore considered it appropriate to specify nivolumab as the sole appropriate comparator therapy in the indication (12).

The RCT KEY-NOTE-040 submitted by the manufacturer with methotrexate, docetaxel and cetuximab as the active comparator was no longer able to provide the data required for a direct comparison with the updated zVT nivolumab. As a result, the G-BA decided on the classification 'added benefit not proven', lower than the 'non-quantifiable' added benefit that the drug had achieved in the IQWiG assessment with the initially used zVT (13, 14).

**Case: Ozanimod (trade name: Zeposia) in multiple sclerosis**

For the present benefit assessment of ozanimod, interferon beta-1a (IFN β-1a) was originally defined as part of the zVT basket in multiple sclerosis in April 2020. At that time, according to the G-BA, the defined zVT basket consisted of Alemtuzumab or fingolimod or natalizumab or, if indicated, a switch within the basic therapeutics (IFN β-1a or interferon beta- 1b (IFN β-1b) or glatiramer acetate, taking into account the marketing authorisation) (15).

As a result of the subsequent oral hearing, IFN β-1a was removed from the zVT basket by decision of the G-BA in January 2021, alt-

**Pembrolizumab (Keytruda)**

| | Studie(n) Name | | Studie(n) Design | Komparator(en) in klinischer Studie |
|---|---|---|---|---|
| Pivotale Studie | KEYNOTE-040 | | Ph III, randomisiert, open-label | Methotrexat, Docetaxel, Cetuximab |
| | Population(en) | zVT | Zeitpunkt | Prozess |
| Erste zVT Wahl | P1* | • Patientenindividuelle Therapie nach Wahl des Arztes (vornehmlich Methotrexat aus der Gruppe der Chemotherapeutika, Strahlentherapie und / oder Operation). | 09/2014 | • G-BA Beratungsgespräch |
| Letzte zVT Wahl | P1* | • Nivolumab | 04/2019 | • Nach Dossiereinreichung |
| | Zusatznutzen | Begründung(en) | | |
| Ergebnis IQWiG Nutzenbewertung Datum: 01/2019 | **P1*: Nicht quantifizierbar** | Zusammenfassend ergibt sich für Erwachsene mit rezidivierendem oder metastasierendem Plattenepithelkarzinom der Kopf-Hals-Region mit PD-L1-exprimierenden Tumoren (TPS ≥ 50 %) und einem Fortschreiten der Krebserkrankung während oder nach vorheriger platinbasierter Therapie ein Anhaltspunkt für einen nicht quantifizierbaren Zusatznutzen von Pembrolizumab gegenüber der zVT Methotrexat. | | |
| Ergebnis G-BA Nutzenbewertung Datum: 04/2019 | **P1*: Nicht belegt** | Die Vergleichstherapie in der Studie KEYNOTE-040 entspricht somit nicht der mit dem vorliegenden Beschluss festgelegten zVT (Nivolumab), weshalb die vorgelegten Ergebnisse eine Bewertung des Zusatznutzens von Pembrolizumab nicht ermöglichen.<br>Im Ergebnis wird festgestellt, dass ein Zusatznutzen von Pembrolizumab nicht belegt ist. | | |

***Fig. 1:*** *Pembrolizumab (Keytruda). Legend: P1* (population 1): adult patients with recurrent or metastatic squamous cell carcinoma of the head and neck region with PD-L1 expressing tumours (TPS ≥ 50 %) and cancer progression during or after previous platinum-based therapy). Source: own presentation.*

hough the submitted RCTs (SUN-BEAM and RADIANCE) contained IFN β-1a as a comparator (16).

This step was considered appropriate by the G-BA in order to adapt the zVT basket to the current state of medical knowledge and the prevailing treatment situation (6). In accordance with the latest medical knowledge, the G-BA generally assumed that patients who do not respond adequately to a basic therapy (interferons or glatiramer acetate) and continue to show high disease activity will be switched more frequently to more effective therapies such as alemtuzumab, fingolimod or natalizumab (16).

With the exclusion of IFN β-1a, a direct comparison between the active comparator of the RCTs and the new zVT defined by the G-BA was no longer possible. As a result, this zVT change meant that the previously determined non-quantifiable added benefit of IQWiG resulted in an unproven added benefit decided by the G-BA (16,17).

**Case: Mepolizumab (trade name: Nucala) in chronic rhinosinusitis with nasal polyps**

Mepolizumab is indicated as adjunctive therapy with intranasal corticosteroids in chronic rhinosinusitis with nasal polyps (CRSwNP) that cannot be adequately controlled with systemic corticosteroids and/or surgery.

Two consultations were held with the G-BA regarding this indication. In the first consultation in December 2016, the G-BA specified treatment with intranasal corticosteroids (budesonide or mometasone furoate) as a zVT. In the second consultation, which took place in July 2020, this CVT was confirmed (18).

As a result of the written and oral statements of the professional societies involved in the benefit assessment (May 2022), it was determined that treatment with intranasal corticosteroids and/or surgery alone is no longer appropriate for this patient group (19).

For its decision on the benefit assessment of mepolizumab, the G-BA also took into account the benefit assessment procedure on dupilumab from May 2020, which had been completed by then. In this procedure, the G-BA assigned a considerable additional benefit to dupilumab compared to the basic therapy with intranasal corticosteroids, which had been considered the standard of care until then (20). The G-BA also noted from the authorisation of omalizumab that high-quality RCTs were available whose results, in combination with the available aggregated evidence, supported the use of omalizumab in the indication to be assessed (21). The statements of the professional societies during the oral hearing for mepolizumab as well as the decision on the benefit of dupilumab and the authorisation of omalizumab prompted the G-BA to adjust the zVT. The zVT was therefore extended from the original intranasal corticosteroids to include the active substances dupilumab or omalizumab.

As a result, the amendment of the zVT by the G-BA led to an unproven added benefit

**Ozanimod (Zeposia)**

| | Studie(n) Name | | Studie(n) Design | Komparator(en) in klinischer Studie |
|---|---|---|---|---|
| Pivotale Studie | SUNBEAM und RADIANCE | | Ph III, randomisiert, Doppelte Verblindung | Interferon Beta-1a (IFN β-1a) |
| | Population(en) | zVT | Zeitpunkt | Prozess |
| Erste zVT Wahl | P1*[a] | • IFN β-1a oder IFN β-1b oder Glatirameracetat oder Ocrelizumab unter Berücksichtigung der Zulassung | 04/2020 | • G-BA Beratungsgespräch |
| | P2*[b] | • Alemtuzumab oder Fingolimod oder Natalizumab oder sofern angezeigt, ein Wechsel innerhalb der Basistherapeutika (IFN β-1a oder IFN β-1b oder Glatirameracetat) | | |
| Letzte zVT Wahl | P1*[a] | • IFN β-1a oder IFN β-1b oder Glatirameracetat oder Ocrelizumab unter Berücksichtigung der Zulassung | 01/2021 | • Nach der mündlichen Anhörung und den schriftlichen Stellungnahmen |
| | P2*[b] | • Alemtuzumab oder Fingolimod oder Natalizumab | | |
| | Zusatznutzen | Begründung(en) | | |
| Ergebnis IQWiG Nutzenbewertung Datum: 10/2020 | P1*[a]: Beträchtlich | In der Gesamtschau liegt ausschließlich ein positiver Effekt in der Kategorie schwerwiegende / schwere Symptome oder Folgekomplikationen vor. Für den Endpunkt bestätigte Krankheitsschübe zeigt sich ein Beleg für einen Zusatznutzen von Ozanimod gegenüber IFN β-1a mit beträchtlichem Ausmaß. | | |
| | P2*[b]: Nicht quantifizierbar | Insgesamt zeigte sich für die Untergruppe der Männer nur ein positiver Effekt in der Kategorie schwerwiegende/schwere Symptome bzw. Folgekomplikationen. Aufgrund der geschlechtsspezifischen Effektmodifikation erfolgt die Ableitung des Zusatznutzens getrennt für Frauen und Männer. | | |
| Ergebnis G-BA Nutzenbewertung Datum: 01/2021 | P1*[a]: Gering | Geringer positiver Effekt von Ozanimod im Vergleich zu IFN β-1a beim Endpunkt bestätigter Krankheitsschübe. Hinsichtlich der Nebenwirkungen besteht ein Vorteil zugunsten von Ozanimod bei einem bestimmten unerwünschtem Ereignis (grippeähnliche Erkrankung). | | |
| | P2*[b]: Nicht belegt | Keine geeigneten Daten im Vergleich zur zVT lagen vor. | | |

***Fig. 2:*** *Ozanimod (Zeposia). Legend: P1(Population 1): adult patients with RRMS who have not yet received disease-modifying therapy or adult patients with RRMS who have been pre-treated with disease-modifying therapy and whose disease is not highly active. RRMS: relapsing-remitting multiple sclerosis. P2(Population 2): adult patients with RRMS with highly active disease despite treatment with a disease-modifying therapy. Source: own presentation.*

**Nucala (Mepolizumab)**

| | Studie(n) Name | | Studie(n) Design | Komparator(en) in klinischer Studie |
|---|---|---|---|---|
| Pivotale Studie | SYNAPSE | | Ph III, randomisiert, open-label | Placebo mit intranasalen Kortikosteroid (Mometasonfuorat) |
| | Population(en) | zVT | Zeitpunkt | Prozess |
| Erste zVT Wahl | P1* | • Intranasalen Kortikosteroiden (Budesonid oder Mometasonfuroat) | 07/2020 | • G-BA Beratungsgespräch |
| Letzte zVT Wahl | P1* | • Dupilumab oder Omalizumab, jeweils in Kombination mit intranasalen Kortikosteroiden (Budesonid oder Mometasonfuroat) | 04/2022 | • Nach mündlicher Anhörung (neuer wissenschaftlicher Kenntnisstand) |
| | Zusatznutzen | Begründung(en) | | |
| Ergebnis IQWiG Nutzenbewertung Datum: 02/2022 | **P1*: Nicht quantifizierbar** | Zusammenfassend gibt es für Patientinnen und Patienten mit schwerer CRSwNP einen Anhaltspunkt für einen nicht quantifizierbaren Zusatznutzen von Mepolizumab als Zusatztherapie mit intranasalen Kortikosteroiden im Vergleich zur zVT. | | |
| Ergebnis G-BA Nutzenbewertung Datum: 05/2022 | **P1*: Nicht belegt** | Es liegen keine geeigneten Daten für die Nutzenbewertung im Vergleich zur zVT vor. | | |

***Fig 3:*** *Fig. 3: Nucala (mepolizumab). Legend: P1* (population 1): Patients with severe CRSwNP that cannot be adequately controlled with systemic corticosteroids and/or surgery. Source: own presentation.*

**Dimethylfumarat (Tecfidera)**

| | Studie(n) Name | | Studie(n) Design | Komparator(en) in klinischer Studie |
|---|---|---|---|---|
| Pivotale Studie | CONNECT | | Ph III, randomisiert, open-label | Interferon Beta-1a (IFN β-1a) |
| | Population(en) | zVT | Zeitpunkt | Prozess |
| Erste zVT Wahl | P1* | • IFN-β 1a oder IFN-β 1b oder Glatirameracetat unter Berücksichtigung des Zulassungsstatus | 09/2021 | • G-BA Beratungsgespräch |
| Letzte zVT Wahl | P1* | • IFN-β 1b oder Glatirameracetat oder Teriflunomid, unter Berücksichtigung des Zulassungsstatus | 11/2023 | • Nach mündlicher Anhörung |
| | Zusatznutzen | Begründung(en) | | |
| Ergebnis IQWiG Nutzenbewertung Datum: 10/2023 | **P1*: Nicht quantifizierbar** | In der Gesamtschau zeigen sich positive Effekte von Dimethylfumarat gegenüber IFN-β 1a für die Endpunkte bestätigte Krankheitsschübe und grippeähnliche Erkrankung (UE) mit dem Ausmaß beträchtlich bzw. nicht quantifizierbar. | | |
| Ergebnis G-BA Nutzenbewertung Datum: 01/2024 | **P1*: Nicht belegt** | Die zVT wurde in der für die Nutzenbewertung vorgelegten Studie nicht umgesetzt. In der Gesamtschau liegen somit keine geeigneten Daten für den Vergleich gegenüber der zVT vor. | | |

***Fig 4:*** *Dimethyl fumarate (Tecfidera). Legend: P1* (population 1): Children and adolescents aged ≥ 13 to < 18 years with relapsing-remitting multiple sclerosis who have not yet received disease-modifying therapy, or children and adolescents pre-treated with disease-modifying therapy whose disease is not highly active. Source: own presentation*

for mepolizumab, as there were no longer any comparative data suitable for the research question of the benefit assessment. IQWiG had previously assessed mepolizumab on the basis of the original zVT basket and found an unquantifiable added benefit (22,23).

**Case: Dimethyl fumarate (trade name: Tecfidera) in multiple sclerosis**

Dimethyl fumarate is approved for the treatment of multiple sclerosis. In February 2022, the G-BA approved interferon β-1a (IFN-β 1a), among others, as a zVT. After the oral hearing in November 2023, the zVTs were adjusted by the G-BA to exclude IFN-β 1a and to newly include teriflunomide (24,25). Thus, the original zVT basket consisted of IFN-β 1a, IFN-β 1b or glatiramer acetate and changed to IFN-β 1b or glatiramer acetate or teriflunomide after the oral hearing.

The decision of the G-BA to change the zVT basket was triggered by a restriction of the marketing authorisation of the European Medicines Agency (EMA) for one of the zVTs originally considered (IFN-β 1a) in the same indication. An extension of the marketing authorisation and the increased therapy site value of teriflunomide also played a role in the G-BA's adjustment of the zVT.

Ultimately, the change in the zVT by the G-BA resulted in the non-quantifiable added benefit initially recommended by IQWiG (based on the previous valid zVT IFN-β 1a) of dimethyl fumarate being changed to an unproven added benefit by the G-BA due to a lack of data for comparison with the new zVT basket (25, 26).

## Discussion

In this analysis, we identified and assessed real-life cases in which the manufacturer was confronted with the situation of an unsuitable study comparator due to a zVT change in the ongoing benefit assessment procedure. This included drugs for the treatment of head and neck tumours, multiple sclerosis or chronic rhinosinusitis, which were denied the additional benefit initially determined by IQWiG in the procedure in the G-BA decision. The examples cited in the analysis illustrate only a fraction of the problem. This is because zVT changes can occur in other cases before the start of the benefit assessment (e.g. lisocabtagene maraleucel, ertugliflozin) and negatively change the assessment result (7). However, further assessment of these cases is difficult to perform as the data are not consistently available or reported to allow consistent analysis (7).

## Impact on the benefit assessment procedures

From the perspective of a researching company, the zVT represents an enormous uncertainty factor for the outcome of the benefit assessment. The G-BA can change it at any time: shortly after the consultation, during an ongoing clinical trial, shortly before or after the submission of a dossier or only with the decision on the outcome of the benefit assessment. This jeopardises the ability to plan, which is essential for research-based companies. At the same time, there is a legal tension between, on the one hand, adapting the therapy standard to medical progress and, on the other hand, demanding the use of the same zVT for therapies of a certain class of active substances in order to ensure a standardised assessment (2).

Changes to the zVT in the ongoing procedure are published in the benefit assessment decision. Changes made before the submission of the dossier are not listed as such in the G-BA's supporting reasons and are not justified. A clear quantification of the frequency is therefore only possible for zVT amendments during the ongoing procedure. In around one in five procedures in the years 2020-2022, changes were made during an ongoing benefit assessment (7). Such changes to the zVT are particularly problematic if they devalue clinical trials for the benefit assessment or render them unusable. This occurs when originally advised zVTs are replaced by a new zVT and the initially defined study comparator is no longer considered a zVT. Despite scientifically high-quality studies, in such cases the manufacturer can no longer prove an additional benefit for formal reasons.

A change in the comparator therapy can lead not only to the invalidation of a clinical trial and the loss of added benefit, but also to the possible strategically intended application of the price guard rails by the GKV-FinStG. For example, when deciding on the benefit assessment of niraparib + abiraterone for the treatment of prostate cancer, the GKV-SV demanded that the zVT be set solely for the combination of olaparib + abiraterone. This step was justified by the fact that olaparib + abiraterone represents the new standard of care for affected patients. The existing clinical trial on abiraterone would then not have been able to formally demonstrate any additional benefit and a possible precedent would have been set with regard to the application of the price guard rails. The National Association of Statutory Health Insurance Physicians (KBV) and the impartial G-BA chairman did not agree to the proposal of the GKV-SV in this procedure and continued to define the zVT with all authorised and benefit-assessed therapies. These include abiraterone or enzalutamide or olaparib (27, 28). The example illustrates well, however, that zVT changes do not only have to follow objective criteria, but that there is always the possibility that they may be strategically intended by the GKV-SV, as they have a direct consequence for price negotiations.

## Conclusion

To summarise, it should be noted that the non-consideration of clinical studies due to changes in the zVT leads to studies of the highest evidence level (RCT) being ignored. This approach cannot be in the spirit of an evidence-based benefit assessment. At the same time, it critically affects investment decisions, the conduct of clinical trials in Germany and, ultimately, healthcare provision.

Comprehensive consultation theoretically offers both parties the opportunity to define the framework for such decision-making. If this framework is implemented sensibly, neither side should be allowed to unilaterally withdraw from the process without commitment or to strategically utilise short-term zVT changes in order to achieve a better starting position for price negotiations. For this reason, the counselling and the specifications for CVT must be more reliable. When determining a comparator therapy, the existing study situation should be taken into account, especially if this was generated by the company on the basis of a G-BA consultation. In this context, those CVTs that are used in a clinical trial after a G-BA consultation should also be used for the assessment of added benefit. If a change in the CVT is urgently required, such additional consideration in the sense of a bridging regulation would improve planning certainty

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in the benefit assessment. At the same time, this would take better account of the best available evidence, while continuing to take appropriate account of the current state of medical knowledge. This would lead to greater acceptance of the clinical trials generated, improve planning certainty for manufacturers and avoid negative effects on healthcare provision. The aim should be to promote evidence-based decision-making. <<

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