FROM EXCEPTION TO OPTION: OFF-LABEL THERAPIES AS COMPARATORS IN GERMAN EARLY BENEFIT DECISIONS UNDER THE ALBVVG FRAMEWORK

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Background

The determination of the appropriate comparator therapy (ACT) by the Federal Joint Committee (G-BA) plays a crucial role in early benefit assessments in Germany. Traditionally, comparator therapies must have marketing authorization for the specific therapeutic indication in accordance with Chapter 5, Section 6 of the G-BA's Rules of Procedure (VerfO). However, the Drug Supply Shortage Control and Supply Improvement Act (ALBVVG), introduced in July 2023, clarifies under which circumstances off-label therapies can be considered as ACT, even when medications lack explicit approval for the intended indication.

Section 6 (2) sentence 3 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) specifies the regulatory basis for such cases (see Box 1 for details). This analysis examines how the G-BA applies the ALBVVG in its decisions and under which conditions the G-BA accepts off-label therapies as ACT.

Box 1: Regulatory Framework - AM-NutzenV Section 6 (2) sentence 3

The G-BA may *exceptionally* determine off-label use as ACT when it represents a *therapy standard* according to the generally recognized state of medical knowledge *and* one of the following applies:

1. It constitutes the therapy standards in the absence of approved alternatives,
2. Off-label use is generally preferable to previously approved medications, or
3. It provides relevant benefits for specific patient groups or indication areas.

Methods

Four benefit assessment procedures from the period following the introduction of the ALBVVG (July 2023 – May 2025), in which off-label therapies were discussed as potential comparators, were exemplarily selected for analysis. The G-BA decisions regarding the choice of ACT were systematically analyzed with a focus on the reasoning provided in the G-BA justification documents (“Tragende Gründe”).

Results

Four benefit assessment procedures demonstrated varying G-BA approaches to off-label therapy acceptance as ACT under the ALBVVG framework.

- For **dupilumab** (pediatric eosinophilic esophagitis, EoE), the G-BA accepted off-label use of budesonide and proton pump inhibitors (PPI) as ACT under AM-NutzenV Section 6 (2) sentence 3 no 1. No approved therapy options exist for this pediatric population, and these therapies prove effectiveness and tolerability in EoE treatment through evidence-based guideline recommendations and clinical practice experience.
- For **midostaurin** (systemic mastocytosis), the G-BA recognized cladribine, imatinib, and avapritinib as ACT under the same legal provision, despite extremely limited evidence due to disease rarity. The G-BA acknowledged that off-label use represents the established therapy standard in the absence of approved alternatives.
- For **lisocabtagene maraleucel** (B-cell lymphomas), the G-BA selectively accepted off-label therapies under AM-NutzenV Section 6 (2) sentence 3 no. 2. Platinum-containing regimens were considered generally preferable to approved alternatives for high-dose therapy eligible patients. For rare lymphoma subtypes, the G-BA accepted specific off-label combinations considering disease severity and their general preference over previously approved medications for the therapeutic indication.
- Conversely, for **talazoparib** (prostate cancer), the G-BA rejected off-label use of abiraterone acetate with prednisone/prednisolone and enzalutamide, determining that available evidence did not support the general preference of off-label use over approved therapeutic options (see Table 1 for an overview).

Table 1: G-BA Off-Label ACT Decisions under ALBVVG Framework

Drug	Off-Label Comparator	G-BA Decision	Legal Basis	Key Decision Factor
Dupilumab (EoE)	Budesonide + PPI	✓ Accepted	First approved medicinal product	No approved alternatives + strong guidelines
Midostaurin (systemic mastocytosis)	Cladribine + Imatinib + Avapritinib	✓ Accepted	First approved medicinal product	Established use + limited evidence
Lisocabtagene maraleucel (B-cell lymphomas)	Platinum regimens + PD-1 inhibitors	✓ Selective	Generally preferable	Disease severity + rare subtypes
Talazoparib (prostate cancer)	Abiraterone + Enzalutamide	✗ Rejected	Criteria not met	Adequate approved alternatives

Results (continued)

Our examination of how the AM-NutzenV criteria from Box 1 were applied across these cases revealed that the availability of approved alternatives functioned as the primary determinant.

Based on the case decisions summarized in Table 1, the key decision factors were identified and systematically structured in a comparative matrix (Table 2) to illustrate overarching patterns in the G-BA’s decision-making.

Cases lacking alternatives (dupilumab, midostaurin) achieved acceptance regardless of evidence quality, whereas cases with adequate approved alternatives led to rejection (talazoparib) despite strong guideline support.

Additionally, disease rarity created regulatory flexibility, with the G-BA accepting "extremely limited evidence" for rare diseases (midostaurin) while requiring robust evidence for more common indications.

The two AM-NutzenV criteria also led to different outcomes – the "no approved alternatives" criterion (no. 1) resulted in acceptance, while demonstrating "general preference" over existing alternatives (no. 2) proved more challenging.

This suggests that while ALBVVG provides a legal framework, the hierarchy and weighting of decision factors may vary depending on specific clinical contexts.

Table 2: Key Decision Factor Analysis Matrix

Drug	Approved Alternatives	Disease Rarity/ Severity	Guideline Evidence	Evidence Quality	Clinical Practice Status
Dupilumab (EoE)	✓ None	✓ High	✓ Strong (consistent)	✓ High (SR, Meta-Analyses, individual studies)	✓ Therapy standard
Midostaurin (systemic mastocytosis)	✓ None	✓ Very high (rare)	✗ Limited	✗ Extremely limited	✓ Relevant therapy options
Lisocabtagene maraleucel (B-cell lymphomas)	✗ Available (excluded)	✓ Very high (rare subtypes)	✓ Strong	~ Mixed	✓ Generally preferable (subtypes)
Talazoparib (prostate cancer)	✗ Available	~ Moderate	✓ Strong	~ Evidence insufficient for preference	✓ Established, not generally preferable

Conclusions

The ALBVVG has legally clarified the conditions under which off-label therapies can be considered as suitable comparators in early benefit assessments. The analysis demonstrates that while AM-NutzenV provides specific legal criteria, their practical application in the analyzed cases reveals a hierarchical decision-making pattern where the availability of approved alternatives serves as the primary determinant, overriding other factors such as evidence quality or guideline strength.

However, fixed, universally applicable criteria do not appear to exist; rather, the G-BA makes decisions on a case-by-case basis. Based on these cases, the contextual weighting of decision factors — particularly regarding disease rarity, clinical practice patterns, and evidence — appears to vary across therapeutic areas. This lack of clarity presents challenges in benefit assessment procedures, as comprehensive demonstration is required in each individual case that the off-label therapy complies with the current state of medical knowledge and is recognized within the healthcare provision system.

References

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